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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 405/12, 405/14, 413/12, 403/12, 409/12, 401/12, 209/20, 307/81, A61K 31/405, 31/34, A61P 25/00, 11/06, 37/00

A1

(11) International Publication Number: WO 00/37462

(43) International Publication Date: 29 June 2000 (29.06.00)

(21) International Application Number: PCT/US99/29592

(22) International Filing Date: 14 December 1999 (14.12.99)

(30) Priority Data:
60/112,725 18 December 1998 (18.12.98) US

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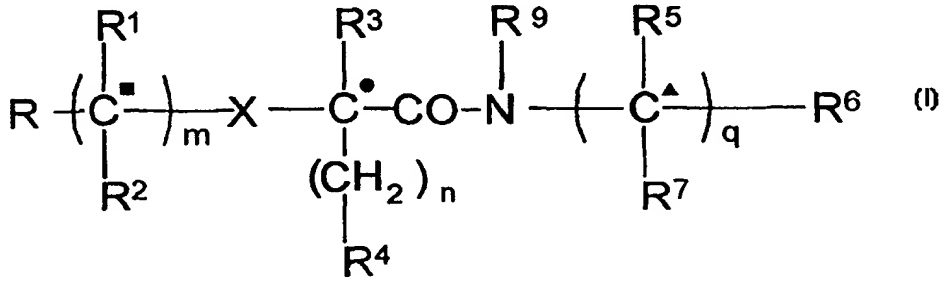
(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NON-PEPTIDE NK_1 RECEPTORS ANTAGONISTS



(I)

(57) Abstract

Non-peptide acetamide derivatives of Formula (I) are specific NK_1 antagonists, where R is aryl, R^1 and R^2 are H or alkyl, m, n and q are integers from 0 to 4, X is NR^8 or NHCONH, R^3 and R^9 are H or alkyl, R^4 is naphthyl or indolyl, R^5 and R^2 are H or alkyl, and R^6 is aryl. The compounds are useful agents for treating inflammatory and allergic disorders, pain, anxiety, depression, schizophrenia and emesis.

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NON-PEPTIDE NK1 RECEPTORS ANTAGONISTS

BACKGROUND OF THE INVENTION

The neurokinins are a family of mammalian neuropeptides that are involved with numerous biological activities such as pain transmission, vasodilation, smooth muscle contraction, bronchoconstriction, activation of the immune system, and neurogenic inflammation. One such neuropeptide known as substance P is widely distributed throughout the peripheral and central nervous system of mammals, and is known to mediate a variety of biological actions via interaction with three neurokinin (NK or tachykinin) receptor types known as NK_1, NK_2, and NK_3.

Substance P binds with higher affinity to the NK_1 receptor than it does to the other receptors. Accordingly, compounds capable of antagonizing the effects of substance P at the NK_1 receptor are useful for treating and controlling disorders mediated by such interactions, including disorders such as anxiety, pain, depression, schizophrenia, and emesis.

Since 1991, a number of high-affinity nonpeptide tachykinin antagonists have been reported; for a review see Sprecher A, *et al* (IDrugs, **1**:73-91, 1998).

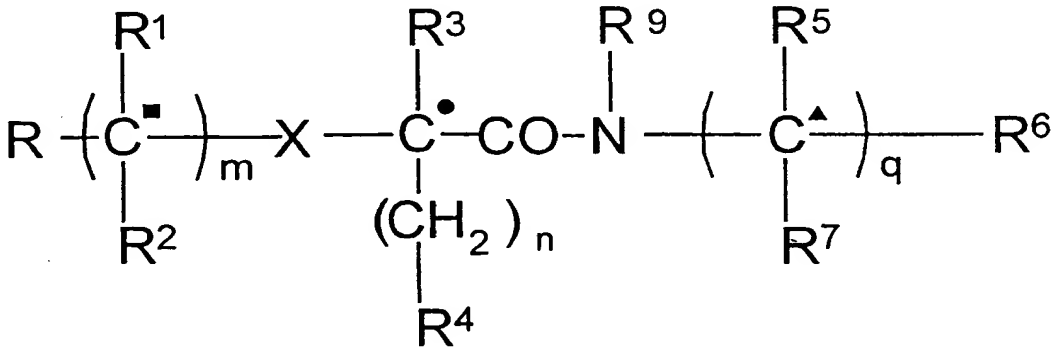
US Patent Nos 5,594,022 and 5,716,979 describe nonpeptides that are relati ·ly specific NK_1 antagonists.

Since substance P mediate various biological actions, including smooth muscle contraction, pain transmission, neuronal excitation, secretion of saliva, angiogenesis, broncho-constriction, activation of the immune system and neurogenic inflammation via an interaction with NK receptors, preferably NK_1, thus compounds capable of antagonising the effects of substance P at NK_1 receptors will be useful in treating or preventing a variety of: brain disorders including pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity and addiction disorders; inflammatory diseases such as arthritis, asthma, bronchitis and psoriasis; gastrointestinal disorders including colitis, Crohn's disease, irritable bowel syndrome, and satiety; allergic responses such as eczema and rhinitis; vascular disorders such as angina and migraine; neuropathological disorders including scleroderma and emesis.

The compounds of the invention, NK_1 receptor antagonists, are useful as anti-angiogenic agents for the treatment of conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth. They will also be useful as agents for imaging NK_1 receptors in vivo in conditions such as ulcerative colitis and Crohn's disease.

SUMMARY OF THE INVENTION

This invention provides NK_1 receptor antagonists characterized as non-peptide acetamide derivatives. The compounds of the invention differ from those of US 5,716,979 or 5,594,022 in that the compounds of Formula I below are not (N-substituted aryl-methyl) carbamates, i.e. they do not have a -O-C(O)-N- link in the backbone; certain final products being more stable than known compounds, they should show improved oral bioavailability and improved CNS penetration. The invention compounds are defined by Formula I:



(I)

and the pharmaceutically acceptable salts thereof, wherein

■, ●, and ▲ indicate all stereoisomers,

R is:

pyridyl,

thienyl,

furyl,

pyrrolyl,

pyrazolyl,

quinolyl,

isoquinolyl,

naphthyl,

indolyl,

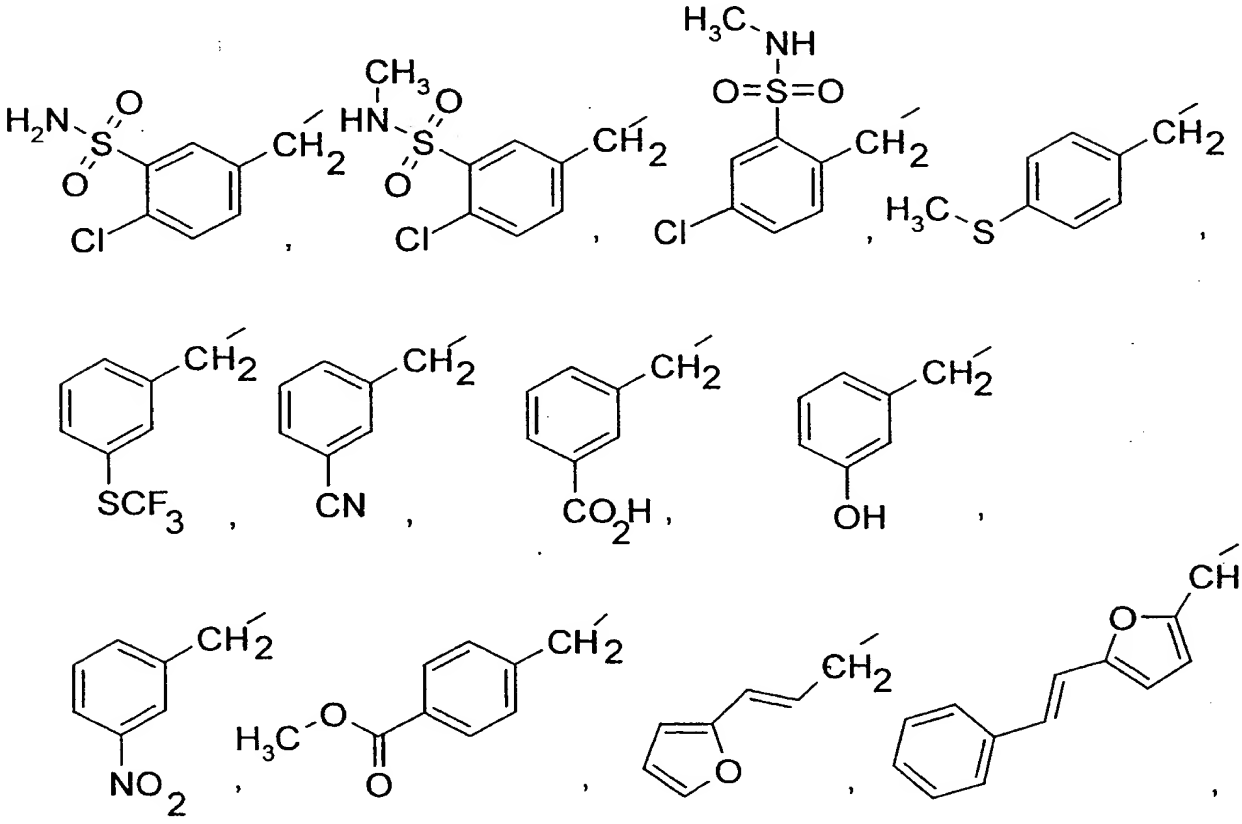
benzofuryl,

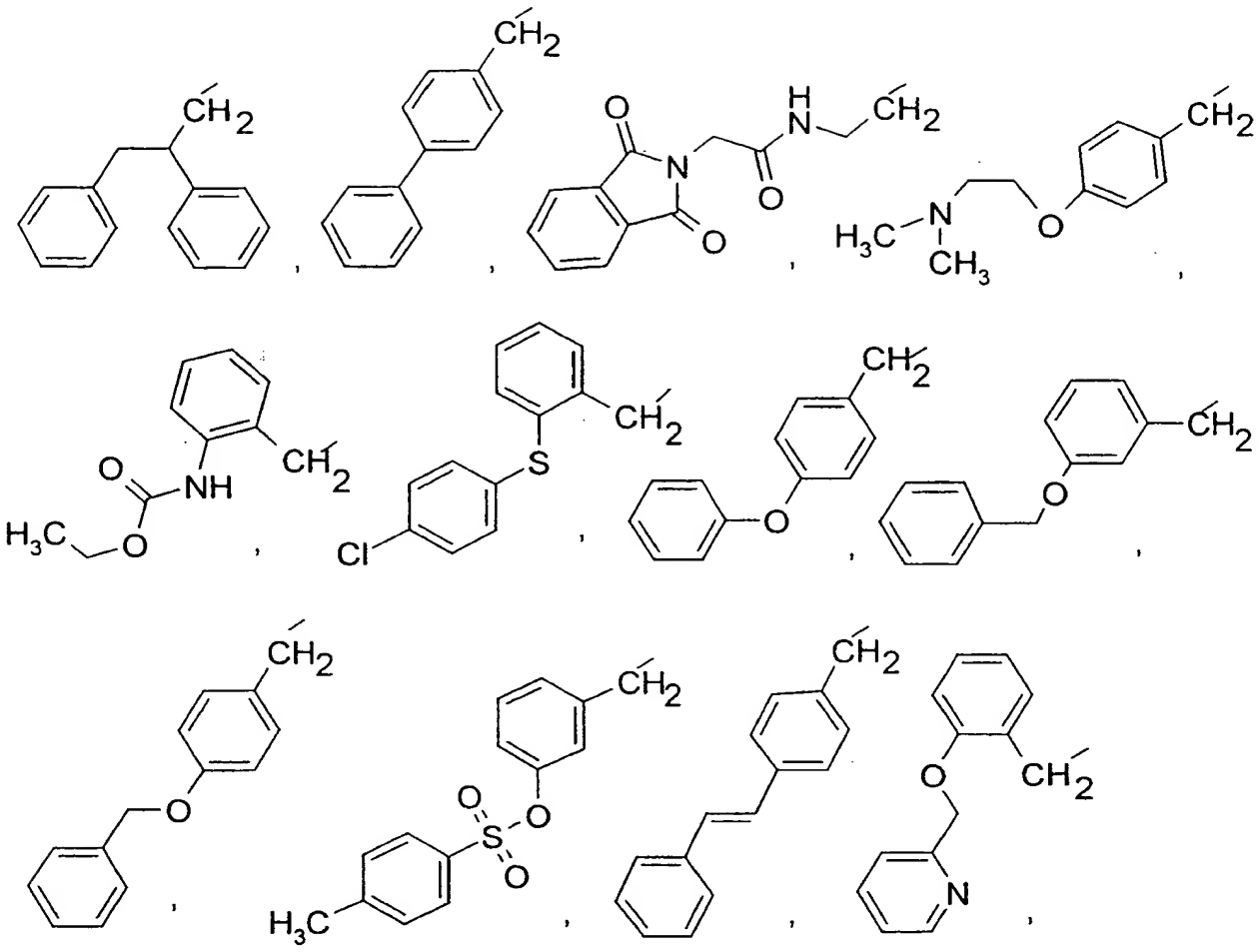
benzothiophenyl,

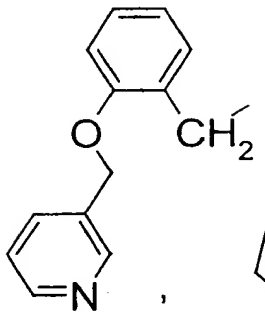
benzimidazolyl, and

benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by alkyl, hydroxy, alkoxy, halogen, $-CF_3$, carboxy, sulfonamide, or nitro;

R can also be:



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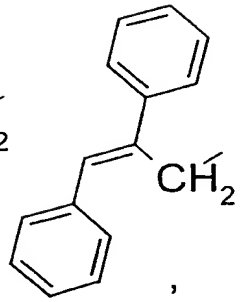
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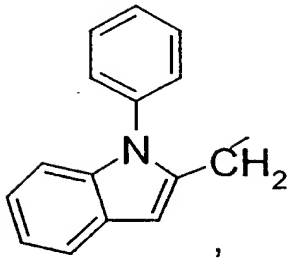
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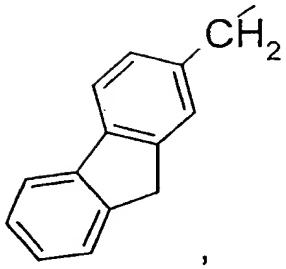
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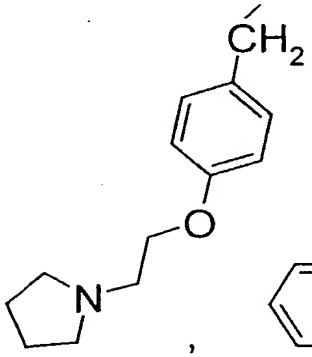
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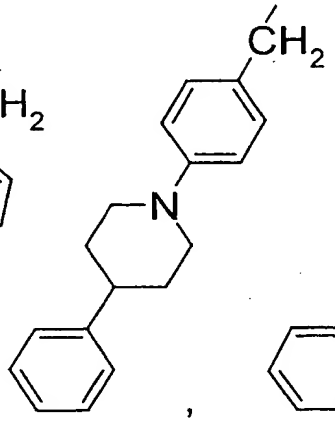
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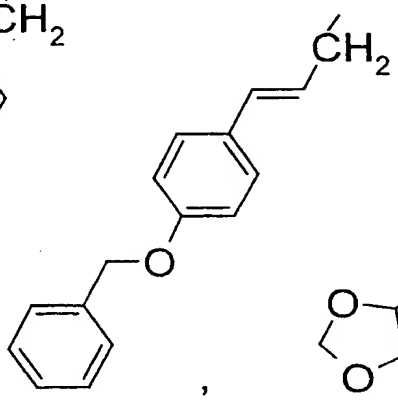
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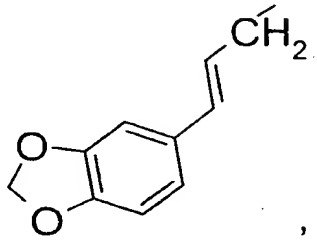
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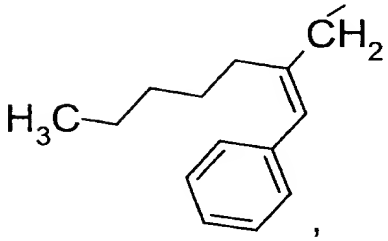
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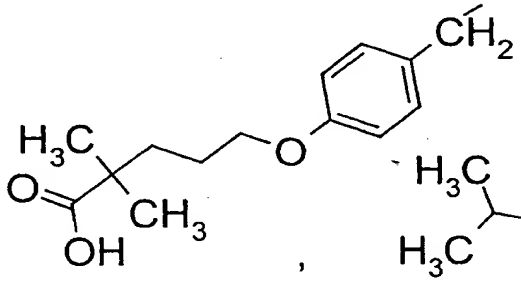
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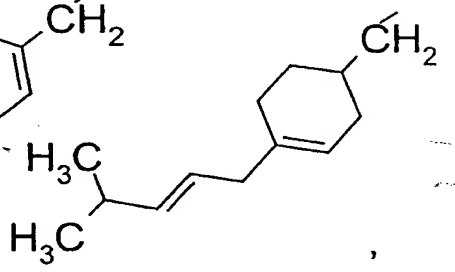
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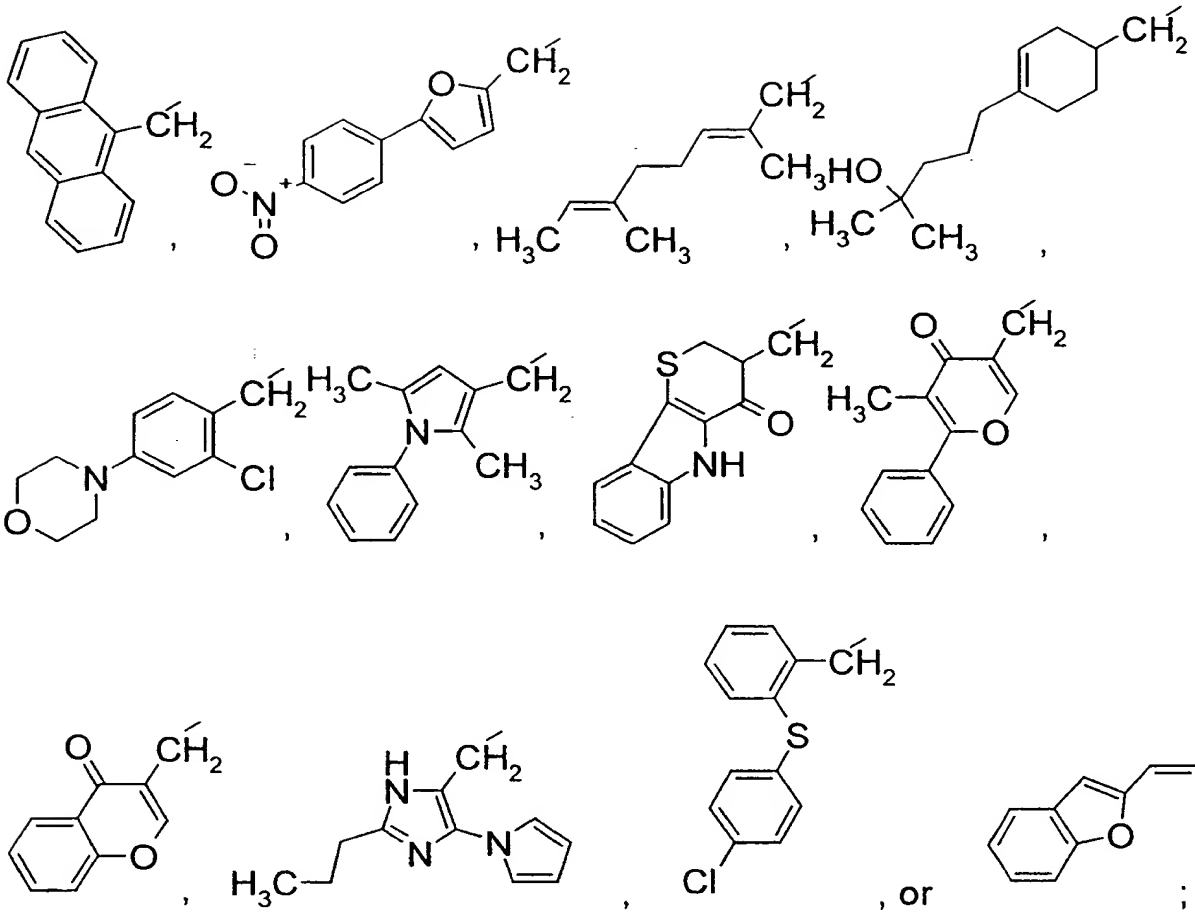


R^1 and R^2 are each independently H or C_1-C_4 alkyl;

m is an integer from 0 to 3;

X is NHCONH , or NR^8 where R^8 is H or C_1-C_4 alkyl;

R^3 is hydrogen or C_1-C_4 alkyl;

n is an integer from 1 to 2;

R^4 is naphthyl or indolyl, wherein said groups are unsubstituted, mono-, di- or trisubstituted by
alkyl, hydroxy or formyl;

R^9 is hydrogen or C_1-C_4 alkyl;

R^5 and R^7 are each independently hydrogen or $(CH_2)_pR^{10}$ where:

p is an integer of 1 to 3, and

R^{10} is H, CH_3, CN, OH, OCH_3, CO_2CH_3, NH_2, $NHCH_3$, or $N(CH_3)_2$;

q is an integer of 0 to 4;

R^6 is phenyl,
pyridyl,
thienyl,
furyl,
pyrrolyl,
pyrazolyl,
imidazolyl,
quinolyl,
isoquinolyl,
naphthyl,
indolyl,
benzofuryl,
benzothiophenyl,
benzimidazolyl, or
benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by alkyl,
hydroxy,
alkoxy,
halogen,
CF_3,
NO_2,
$N(CH_3)_2$,
OCF_3,
$SONH_2$,
NH_2,
$CONH_2$,
CO_2CH_3, or
CO_2H,
or R^6 is:
straight alkyl of from 1 to 3 carbons,

branched alkyl of from 3 to 8 carbons,

cycloalkyl of from 5 to 8 carbons or

heterocycloalkyl,

each of which can be substituted with up to one or two substituents selected from

OH,

CO_2H,

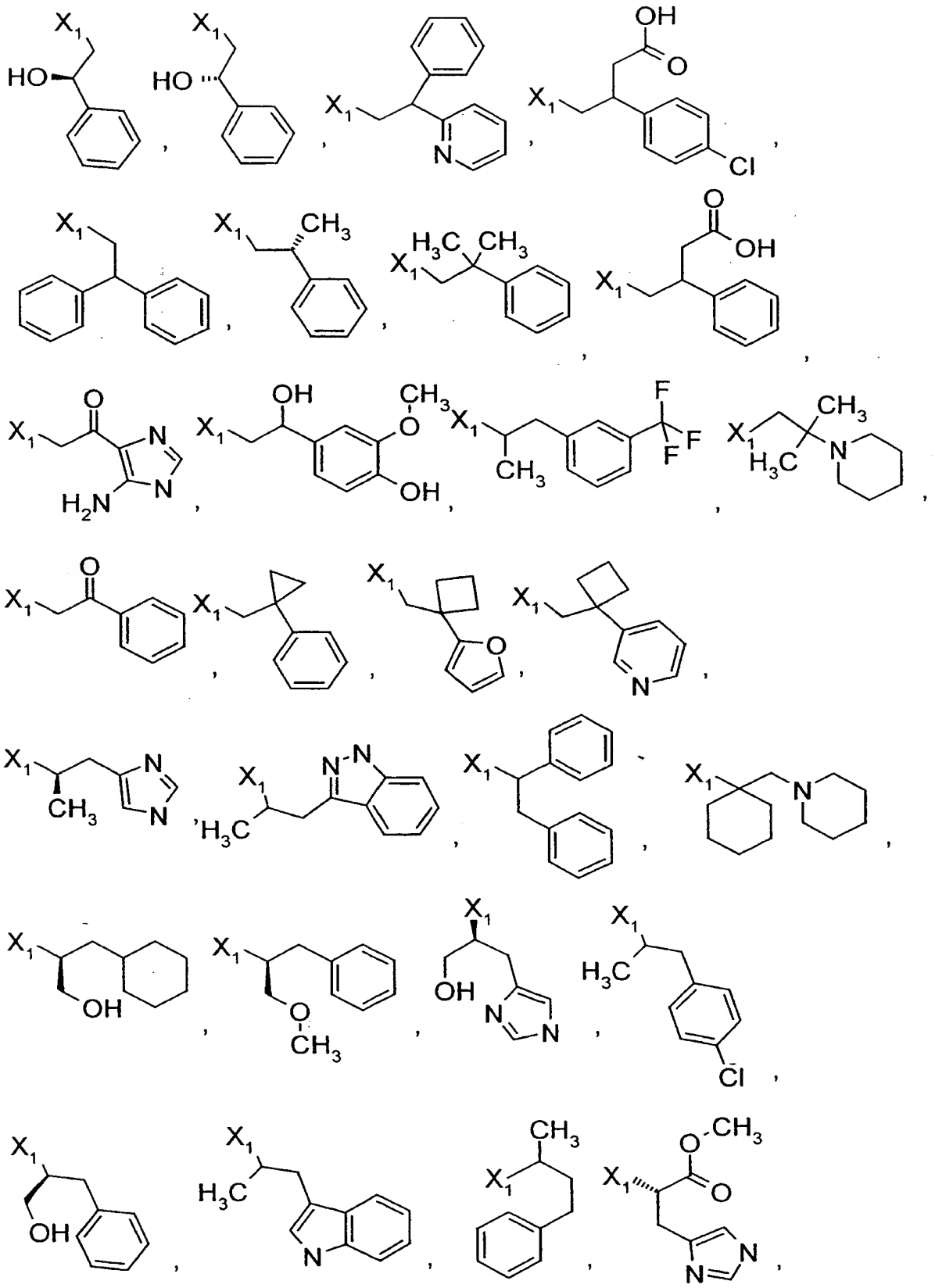
$N(CH_3)_2$,

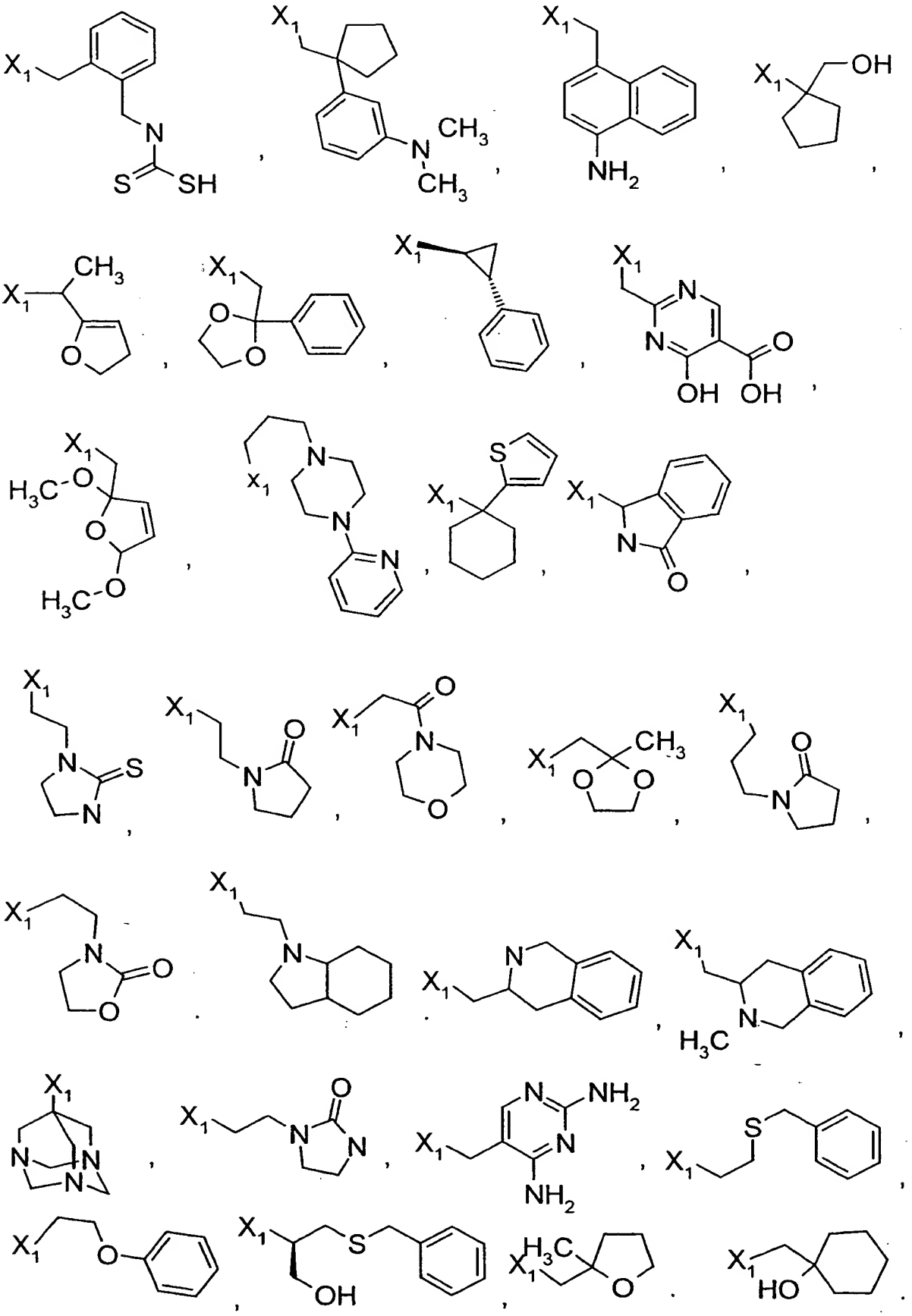
$NHCH_3$ and

CH_3; and

R^5 and R^6, when joined by a bond, can form a ring;

R^6 is also



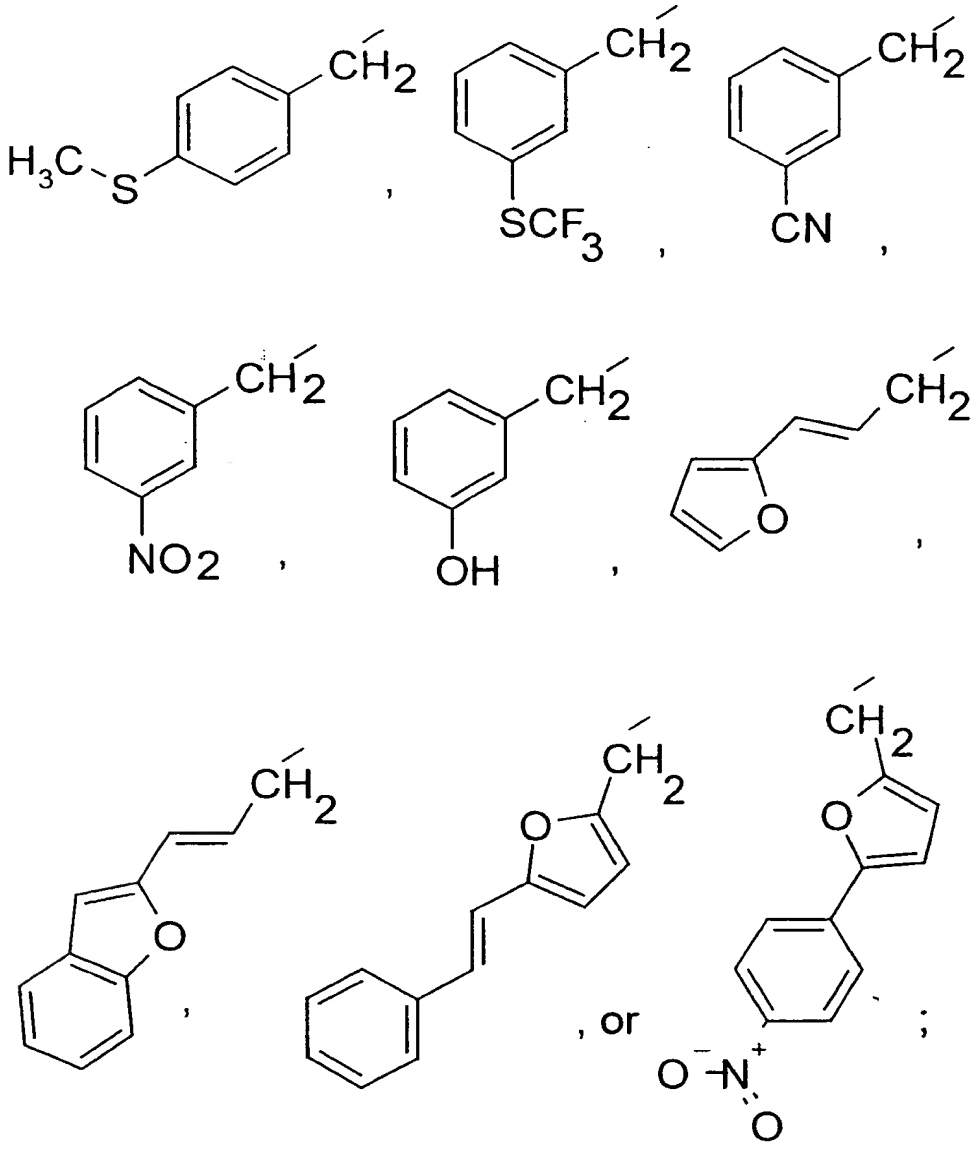


where X_1 represents the rest of the molecule.

Prodrugs of the above are also contemplated such as would occur to one skilled in the art; see Bundgaard, *et al*, Acta Pharm Suec, 1987; **24**: 233-246. For example, a suitable moiety may be attached to a nitrogen of the linker X, to the nitrogen of the NR^9 linker, or that of an indolyl radical of R^4.

Preferred compounds of the invention are those of Formula I above wherein

R is pyridyl,
thienyl,
furyl,
quinolyl
isoquinolyl
naphthyl,
indolyl,
benzofuryl,
benzothiophenyl,
benzimidazolyl,
benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by alkyl, hydroxy, alkoxy, halogen, or CF_3,



m is an integer from 1 to 3;

R^6 is phenyl
pyridyl,
thienyl,
furyl,
pyrrolyl,
quinolyl,
isoquinolyl,
naphthyl,
indolyl,

benzofuryl,
benzothiophenyl,
benzimidazolyl, or
benzoxazolyl,
wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by
alkyl,
hydroxy,
alkoxy,
halogen,
CF_3,
NO_2
$N(CH_3)_2$,
OCF_3,
$SONH_2$,
NH_2,
$CONH_2$,
CO_2CH_3, or
CO_2H,

cycloalkyl of from 5 to 6 carbons or heterocycloalkyl, with up to one or two substituents selected from OH,
CO_2H,
$N(CH_3)_2$,
$NHCH_3$ and
CH_3 ; and

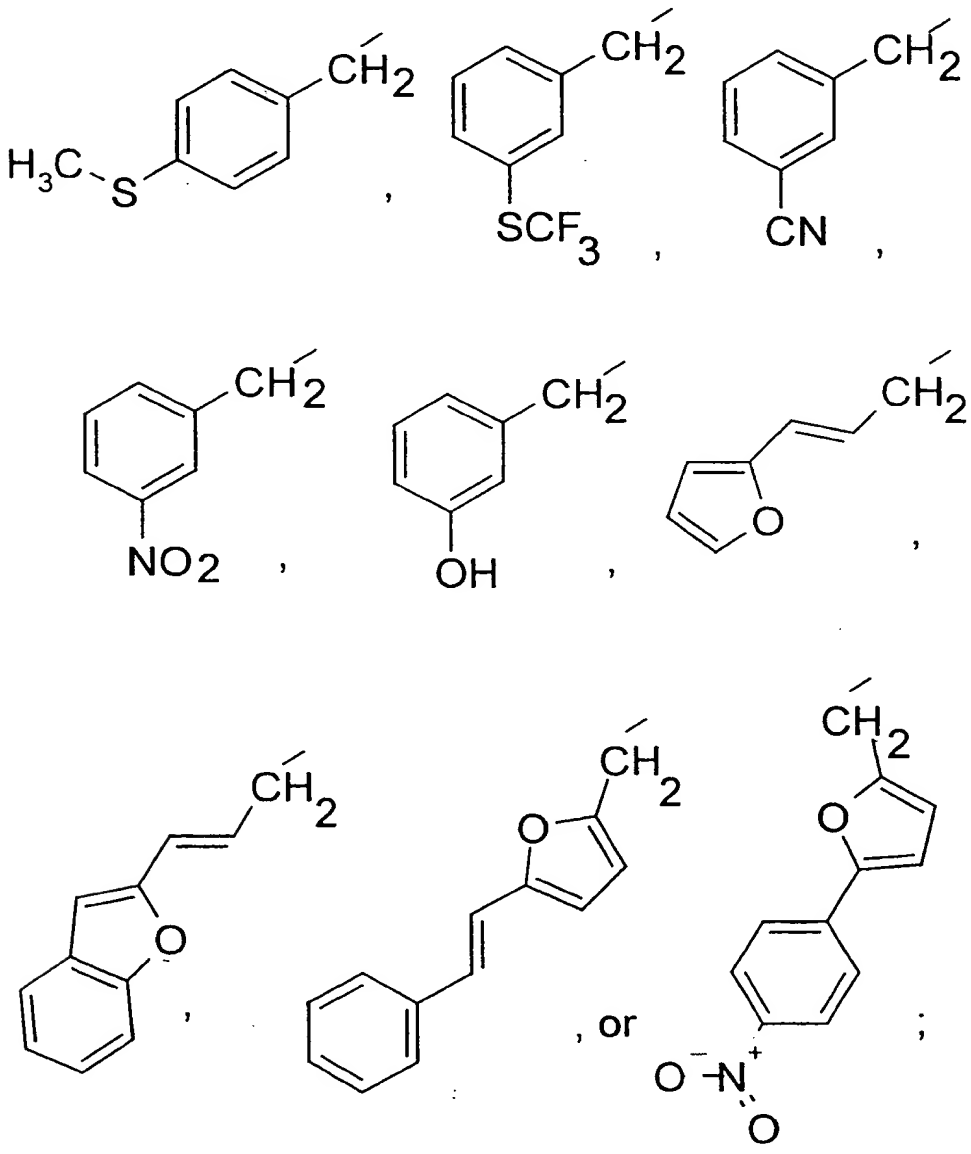
R^5 and R^6 when joined by a bond can form a ring.

More preferred compounds of the invention are those of Formula I above wherein
R is pyridyl,
thienyl,
furyl,
quinolyl,
naphthyl,
benzofuryl,

benzothiophenyl,

benzimidazolyl, or

benzoxazolyl, where each of the foregoing is unsubstituted, mono-, di- or trisubstituted by alkyl, hydroxy, alkoxy, halogen, or-CF_3 ,



R^1 and R^2 are each H;

m is an integer from 1 to 3;

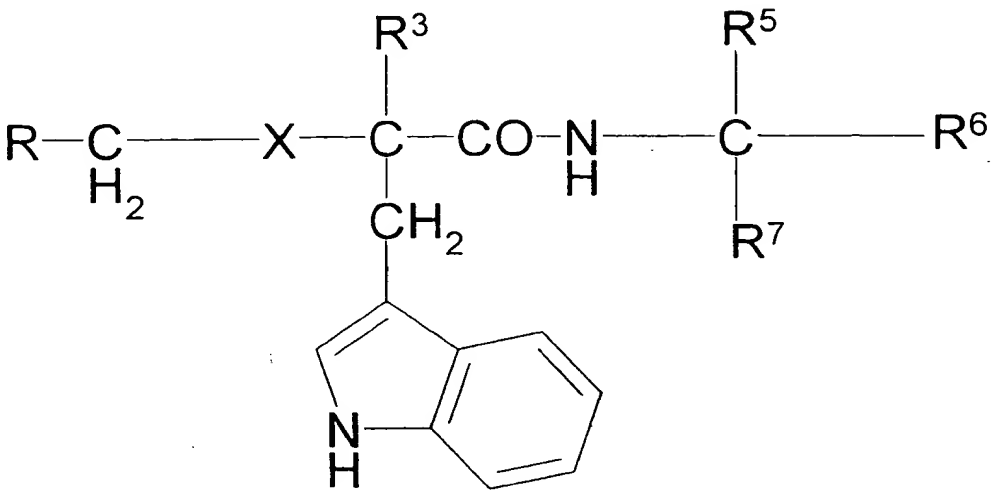
X is NR^8 or NHCONH, where R^8 is H or methyl;

R^9 is hydrogen or alkyl of 1 to 3 carbon atoms;

R^6 is phenyl,
pyridyl,
thienyl,
furyl,
pyrrolyl,
benzimidazolyl, where each of the foregoing is unsubstituted, mono-, di- or trisubstituted by
alkyl,
hydroxy,
alkoxy,
halogen,
CF_3,
NO_2,
$N(CH_3)_2$;
cyclohexyl or heterocycloalkyl, with up to one or two substituents selected from
OH,
CO_2H,
$N(CH_3)_2$,
$NHCH_3$ and
CH_3; and

R^5 and R^6, when joined by a bond, can form a ring.

The most preferred compounds of the invention have Formula II:



(II)

wherein:

R is benzofuryl,
benzoxazolyl,
3-cyanophenyl,
3-nitrophenyl, or
3-trifluoromethylphenyl;

R^3 is hydrogen or methyl;

X is NH or NHCONH;

R^5 and R^7 independently are hydrogen or CH_2R^{10}, where R^{10} is H, CH_3 or OH;

R^6 is phenyl,
substituted phenyl,
pyridyl, or,
cyclohexyl;

and the pharmaceutically acceptable salts thereof.

Most preferred compounds of the invention are:

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-4-yl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-(4-nitro-phenyl)-ethyl]-propionamide, [R-(R*,R*)]

2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-1-phenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide, [R-(R*,R*)]

[R-(R*,S*)]2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide

[R-(R*,S*)]2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-p-tolyl-ethyl)-propionamide

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-p-tolyl-ethyl)-propionamide, [R-(R*,S*)]

2-(3-Cyano-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

3-(1H-Indol-3-yl)-2-(3-nitro-benzylamino)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-(3-trifluoromethoxy-benzylamino)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-pyridin-4-yl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzoxazol-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide

2-(2-Benzofuran-2-yl-ethylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)], and

2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)].

The invention additionally provides pharmaceutical formulations comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier, diluent or excipient therefor. Especially preferred formulations comprise a compound of Formula II.

The invention also provides a method for antagonizing NK_1 receptors in a mammal comprising administering to a mammal an NK_1 binding amount of a compound of Formula I.

The invention further provides a method for treating a CNS disorder including pain, anxiety; depression, obesity, or schizophrenia; an allergic or inflammatory disease; a gastrointestinal disorder; a vascular disorder; or a neuropathological disorder including emesis; comprising administering to a mammal in need of treatment an effective amount of a compound of Formula I. An especially preferred method of treatment utilizes a compound of Formula II.

DETAILED DESCRIPTION OF THE INVENTION

Throughout this application, the following abbreviations have the meanings listed below:

Boc	tertiary butyloxycarbonyl
DCE	dichloroethane
DCM	dichloromethane
HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
DIPEA	N,N-diisopropylethylamine
DMF	N,N-dimethylformamide
DCC	1,3-dicyclohexylcarbodiimide
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EtOAc	ethyl acetate
EtOH	ethanol
MeOH	methanol
KOH	potassium hydroxide
DIBAL	Diisobutylaluminium hydride
NMM	N-methyl-morpholine
NMR	nuclear magnetic resonance
Trp	Tryptophan

The term "alkyl" means a straight or branched hydrocarbon having from one to 12 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, undecyl, dodecyl, and the like unless stated specifically otherwise.

The term "cycloalkyl" means a saturated hydrocarbon ring which contains from 3 to 12 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl except as otherwise stated.

The term "alkoxy" means an alkyl as described above attached through an oxygen atom.

The term "halogen" is chlorine, bromine, fluorine or iodine.

The ring formed by joining R^5 and R^6 is from 4 to 6 atoms total and is unsubstituted.

The compounds of Formula I are capable of forming pharmaceutically acceptable acid addition salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compound of Formula I include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like as well as the salts derived

from nontoxic organic acids, such as the aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy-alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandalate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like. For example, see Berge S.M., *et al.*, Pharmaceutical Salts, J. Pharm. Sci., **66**:1-19 (1977) incorporated herein by reference.

The acid addition salts of the compounds of Formula I are prepared by contacting the free base form of the compound with a sufficient amount of the desired acid to produce the salt in the conventional manner. Preferably, a compound of Formula I can be converted to an acidic salt by treating an aqueous solution of the desired acid, such that the resulting pH is less than four. The solution can be passed through a C18 cartridge to absorb the compound, washed with copious amounts of water, the compound eluted with a polar organic solvent such as, for example methanol, acetonitrile, aqueous mixtures thereof, and the like, and isolated by concentrating under reduced pressure followed by lyophilisation. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for the purpose of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. In addition, the compounds of the present invention can be administered by inhalation, for example intranasally. Additionally,

the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of the compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, pills, tablets, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances that may also act as diluents, flavouring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid that is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose sodium carboxymethylcellulose, and other well-known suspending agents.

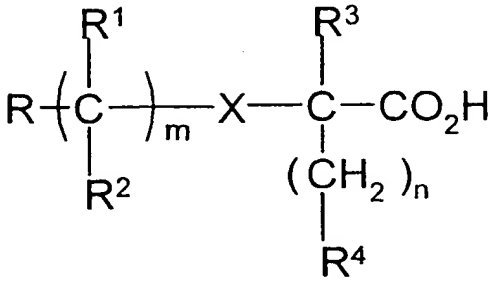
Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet or lozenge itself, or it can be the appropriate number of any of these in packaged form.

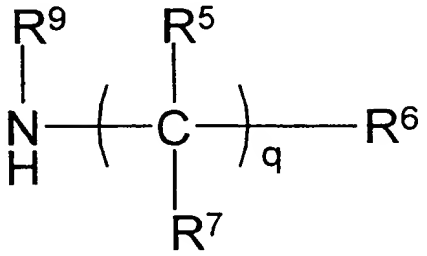
The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 200 mg, preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use, the highly selective and competitive antagonists of the NK_1 receptor and compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg/kg to about 500 mg/kg daily. A daily dose range of about 0.01 mg/kg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller doses, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The compounds of Formula I can be prepared by any several synthetic processes well known to those skilled in the art of organic chemistry.



In a typical synthesis, a carboxylic acid of the formula is



coupled to an amine of the formula

The coupling can be achieved by routine acylation, e.g. by converting the acid to an acid halide, followed by reaction with the amine, or by utilizing a common coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ). The synthesis can be carried out on racemic reactants, to provide invention compounds in racemic form, which can then be resolved by conventional methods, if desired. Alternatively, the invention compounds can be prepared in optically active form by using enantiomeric reactants.

In a typical synthesis, an optically active acetic acid is first prepared by conventional methods.

Schemes 1-5 illustrate the preparation of intermediates utilized in Examples 1-5, which illustrate the synthesis of specific compounds of Formula I in optically active form.

Scheme 1 describes the synthesis of intermediates I and II, which are required for Examples 1 to 5. The N-terminal benzofuran moiety is introduced by the reductive amination of either tryptophan methyl ester or alpha-methyl-tryptophan methyl ester with benzofuran-2-carboxaldehyde and sodium triacetoxy borohydride in DCM. The methyl ester is then hydrolyzed to the corresponding carboxylic acid with lithium hydroxide.

Scheme 2 describes the synthesis of intermediate III. 3-Acetyl-1-methyl pyrrole is converted to the corresponding oxime by reaction with hydroxylamine sulfate and potassium hydroxide in water/methanol. The oxime is then reduced on palladium on carbon.

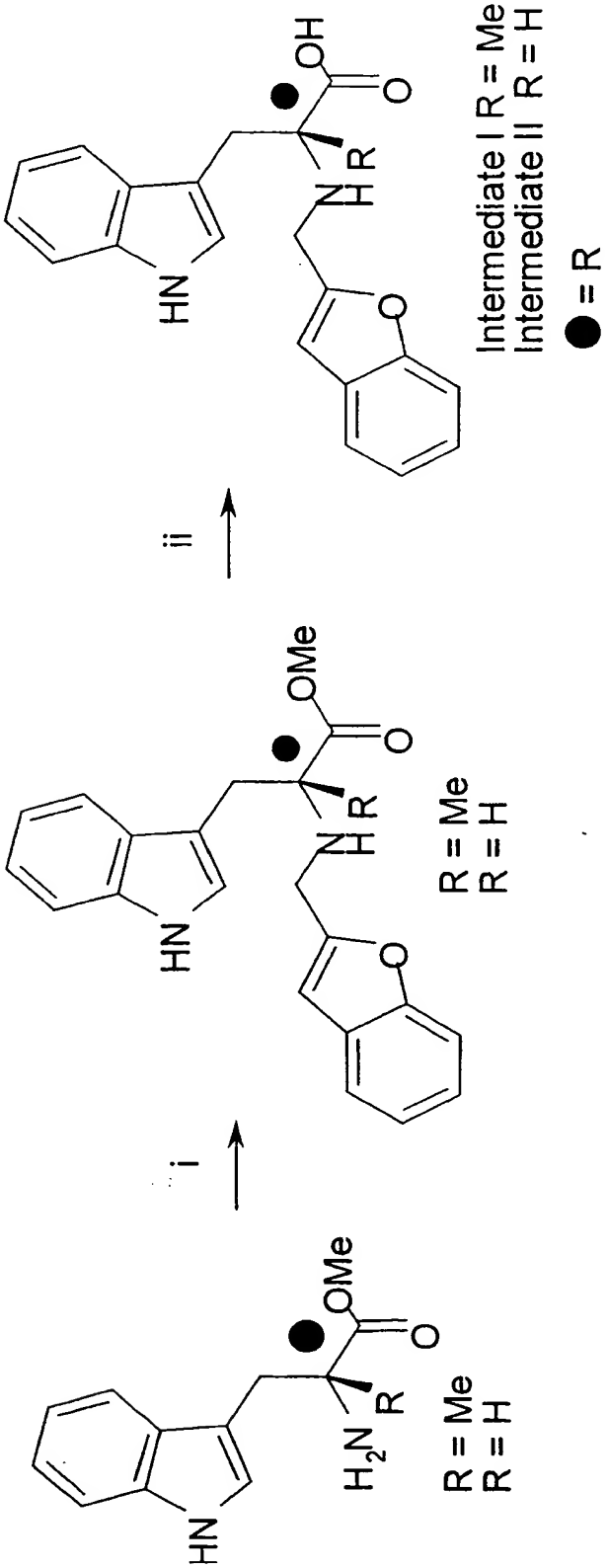
Scheme 3 shows the synthesis of intermediate IV. This compound was prepared from (R)-2-phenylglycinol, which was first N-terminal protected as the carbobenzoxy (CBZ)

analogue. The alcohol was then treated with triethylamine and methane sulfonylchloride, followed by dimethylamine to introduce the tertiary amine. Removal of the CBZ protection with hydrogen over Pearlman's catalyst gave the required intermediate.

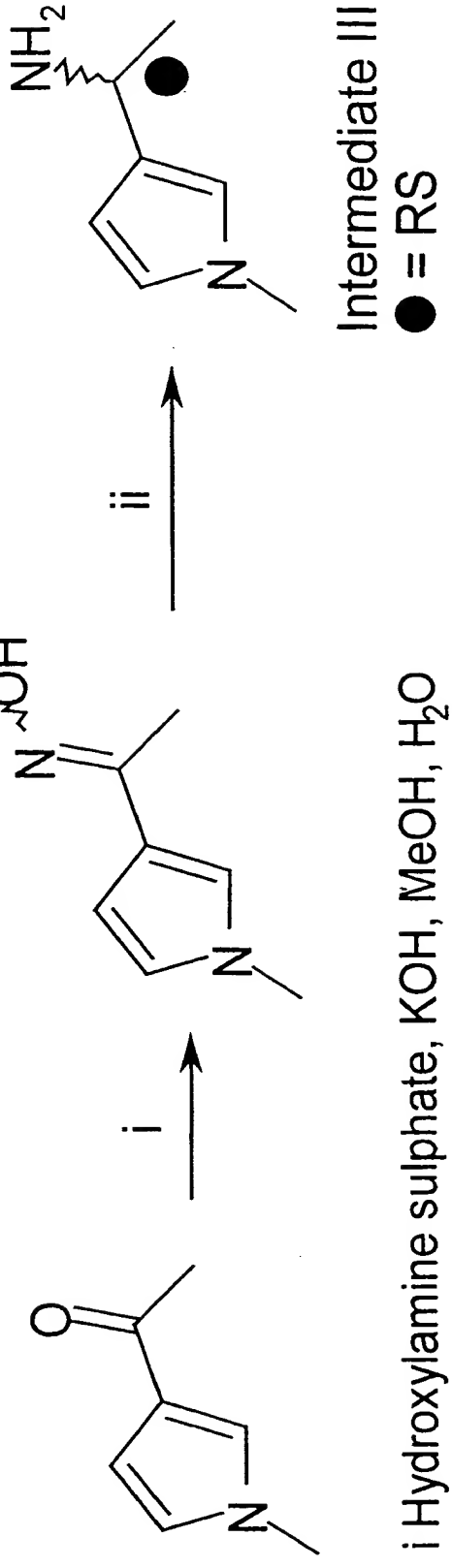
Scheme 4 describes the synthesis of Examples 1 to 4. Each was prepared by activation of the acid, intermediate I, with HBTU in the presence of DIPEA and then reacting with the required amine in DMF.

The synthesis of Example 5 is outlined in scheme 5. Intermediate I was activated with HBTU in DMF and then coupled with methoxybenzylamine. The methyl ether was then reduced with boron tribromide in DCM.

Scheme 1

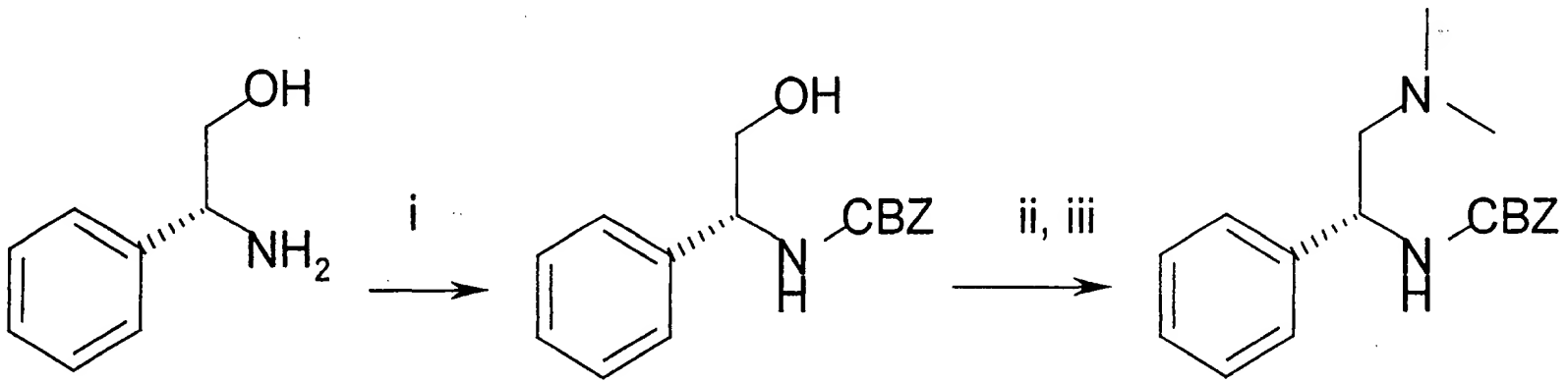


i Benzofuran-2-carboxaldehyde, Sodium triacetoxy borohydride, DCM
ii LiOH, H_2O



Scheme 2.

Scheme 3.

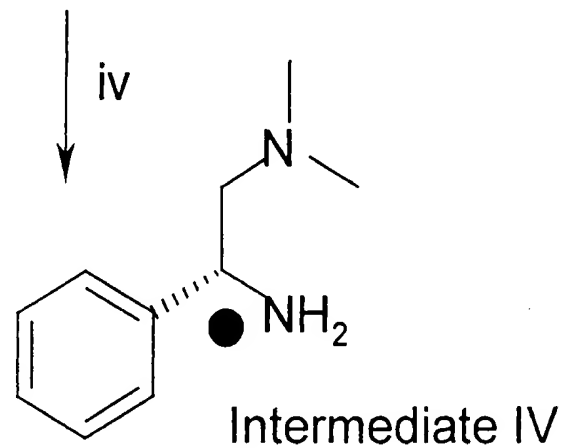


i Benzyl chloroformate, Et_3N,THF

ii CH_3SO_2Cl, Et_3N, THF

iii 2M $HNMe_2$, in THF

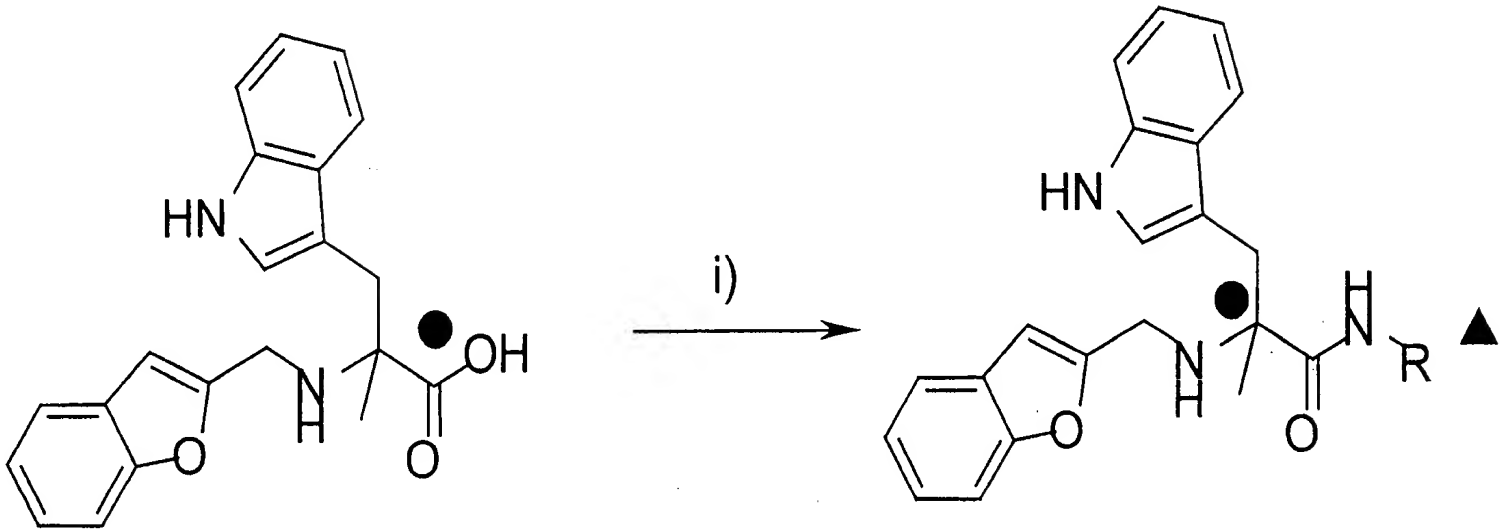
iv H_2, Pearlman's cat., MeOH



Intermediate IV

● = R

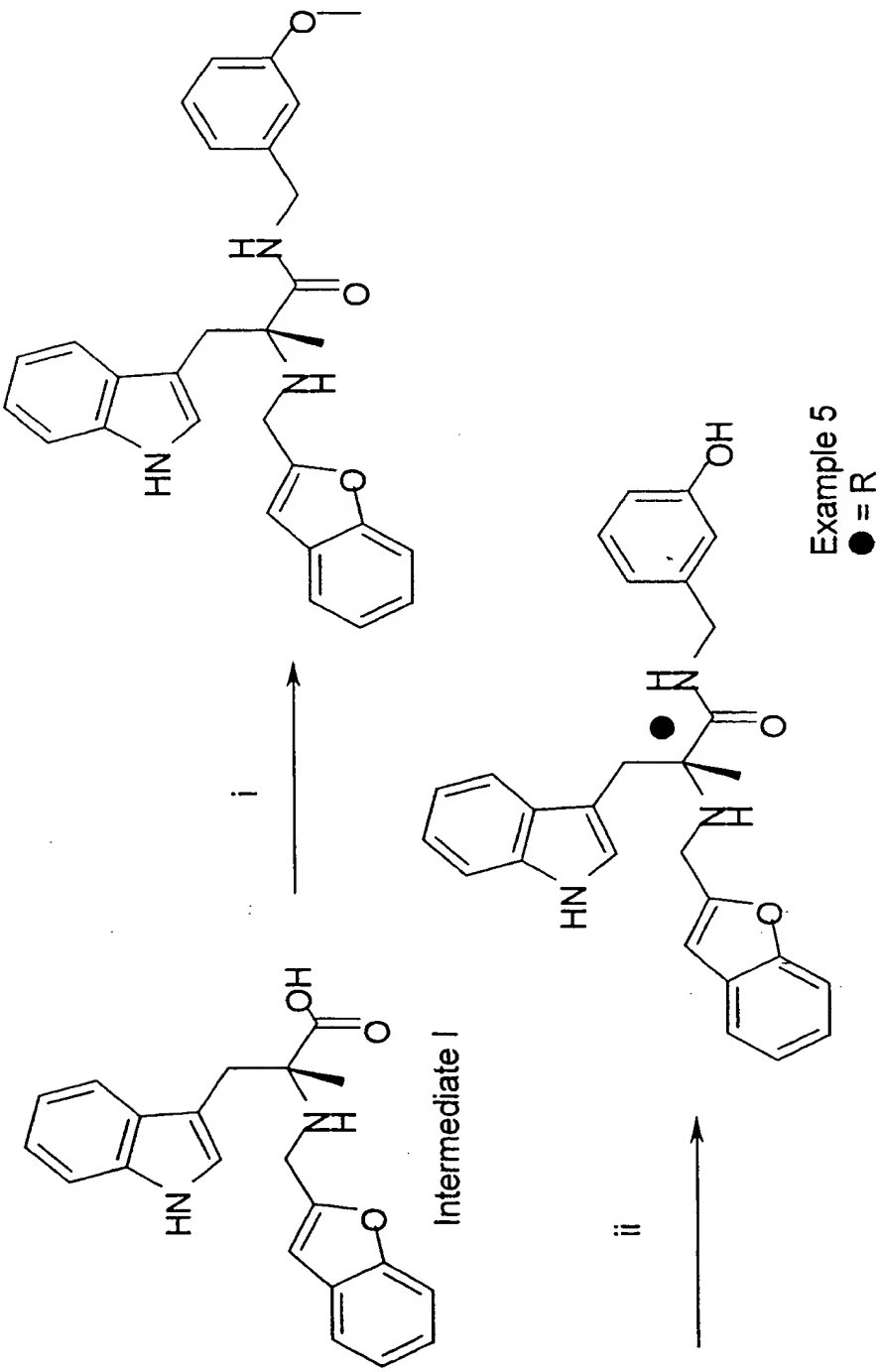
Scheme 4



i) amine, HBTU, DIPEA, DMF

Example number	●	▲	Amine (RNH_2)
1	R	-	$NH_2C(CH_3)_2Ph$
2	R	RS	Intermediate III
3	R	S	$NH_2CH(CH_3)$4-pyridine
4	R	R	Intermediate IV

Scheme 5


Intermediate I
Example 5
● = R
i
ii
i HBTU, DIPEA, Methoxybenzylamine, DMF
ii BBr_3, DCM

EXAMPLE 1.

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-methyl-1-phenyl-ethyl)-propionamide, (R)

Step 1.

Alpha methyl tryptophan methyl ester (26.8g, 0.115mol) and benzofuran-2-carboxaldehyde (17.57g, 0.115mol) were dissolved in DCM (400mL) under an atmosphere of nitrogen and sodium triacetoxyborohydride (34.12g, 0.161mol) was added portionwise over 20 min at 0°C. The mixture was stirred at room temperature for 2 h and then quenched by the addition of sat. $NaHCO_3$ (500mL). The organic layer was collected and the aqueous layer was extracted three times with EtOAc. The organics were combined, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was crystallized from ether/heptane to give the product (34.13g, 82%); IR (film): 3410, 2948, 1724, 1455, 1253, 1104, 742cm^{-1}; NMR ($CDCl_3$)δ 1.48 (3H, s); 3.18 (1H, d, J=14 Hz); 3.21 (1H, d, J=14 Hz); 3.53 (3H, s); 3.85 (1H, d, J=1 Hz); 3.92 (1H, d, J=14 Hz); 6.55 (1H, s); 7.04-7.59 (9H, m); 8.07 (1H, s); MS; ES+ 363, ES- 361.

Step 2. Intermediate I

The methyl ester from step one (24.94g, 68.8mmol) was dissolved in dioxan (800mL) and aq. LiOH (8.66g, 206 mmol in 400mL) was added. The reaction mixture was stirred overnight at room temperature and then heated to 60°C for 5 h. The mixture was reduced *in vacuo* to a volume of approximately 200ml. Water (1200mL) was added and the reaction was stirred vigorously while it was neutralized with 1N HCl. Ether (1200mL) was added and the mixture was stirred for two h, the precipitate was filtered off, washed with water, ether and dried to give a white solid; (24.5g, 100%); NMR (Dmso-d_6) 1.28 (3H, s); 3.05 (1H, d, J=14 Hz); 3.07 (1H, d, J=14 Hz); 3.33 (2H, br s); 3.87 (2H, s); 6.72 (1H, s); 6.97-7.07 (3H, m); 7.14 (1H, d, J=2Hz); 7.18-7.33 (3H, m); 7.50-7.58 (3H, m); 10.89 (1H, s); MS; ES+ 349, ES- 347.

Step 3.

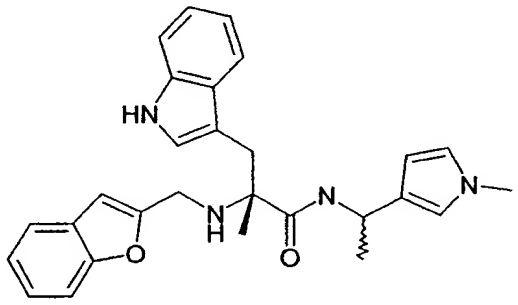
Intermediate I (0.348 g, 1 mmol), HBTU (0.379 g, 1 mmol), DIPEA (0.35 mL, 2 mmol) and cumylamine (0.20 g, 1.48 mmol) were stirred in DMF (25 mL) for 18 h. The reaction mixture was evaporated and the residue taken up in EtOAc and washed with 10% Na_2CO_3, and brine.

Drying and purification by column chromatography using 20% EtOAc/Heptane gave a white solid (0.285 g, 61%). mp=57-62°C;

NMR ($CDCl_3$): δ 1.40 (3H, s); 1.70 (6H, s); 1.92 (1H, b s); 3.17 and 3.22 (2H, 2x d, J=14.4,14.6); 3.82 and 3.89 (2H, 2xd, J=14.6, 14.1); 6.46 (1H, s); 7.02-7.68 (15H, m); 8.10 (1H, s); IR (film): 3317,2987, 1661, 1506, 1455cm^{-1}; $[\alpha]_D^{23}$= 26.1° (c=1, MeOH); MS(ES^+) 466 (M+1); Analysis calculated for $C_{30}H_{31}N_3O_2$. 0.25H_2O: C, 76.65; H, 6.75; N, 8.94%. Found: C, 76.73; H, 6.54; N, 8.80%.

EXAMPLE 2.

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-(1-methyl-1H-pyrrol-3-yl)-ethyl]-propionamide, [R-(R*,R*)] and [R-(R*,S*)]



Step 1

3-Acetyl-1-methyl pyrrole (2.00g, 16.2mmol) was dissolved in MeOH (60 mL) and treated with potassium hydroxide (4.10g, 73 mmol) in water (10mL) and hydroxylamine sulfate (4.00g, 24.3mmol) in water (10mL) and stirred for 18 h. The methanol was removed *in vacuo* and the residue was diluted with water and extracted with EtOAc. Drying ($MgSO_4$) and evaporation gave an off-white solid (1.82g, 81%). (E:Z = 9:1); NMR ($CDCl_3$): δ 2.17 (3H, s); 3.65 (3H, s); 3.69 (3H, s); 6.39 (1H, m); 6.46 (1H, m); 6.56 (1H, m); 6.58 (1H, m); 6.85 (1H, m); 7.59 (1H, m); 8.10 (1H, bs); IR(film): 3240, 2916, 1644, 1554, 1422, 1257, 892cm^{-1}.

Step 2 Intermediate III

The oxime from step one (0.25g, 1.8mmol) was dissolved in methanol and 10% Palladium on carbon (50mg) was added. The mixture was shaken under an atmosphere of hydrogen at 35psi and at 30°C for 5 h. Filtering through Kieselguhr and evaporation gave a colorless oil (220

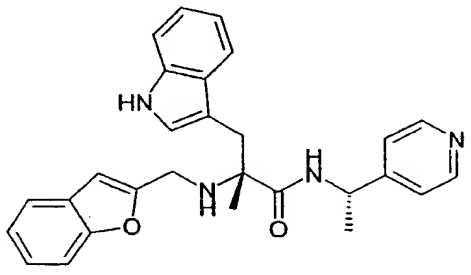
mg) which was a mixture of starting material and product ~1:1. The crude, intermediate III was used in step 3.

Step 3

Intermediate I (0.348g, 1mmol), HBTU (0.379g, 1mmol), DIPEA (0.35mL, 2mmol) and the amine (Intermediate III) (220mg, 1.8mmol) were stirred in DMF (13mL) for 18 h. The reaction mixture was evaporated and the residue taken up in EtOAc and washed with 10%Na_2CO_3, and brine. Drying and purification by column chromatography using 20% EtOAc/Heptane followed by reverse phase chromatography using 50-100% MeOH/H_2O gave a white solid (0.205g, 45%); mp= 53-57°C; NMR ($CDCL_3$): δ 1.35 and 1.43 (3H, 2xd, J=6.6 and 6.6Hz); 1.45 (obs H_2O) and 1.5 (3H, 2xs); 1.89 (1H, bs); 3.21 and 3.22 (2H, 2xs); 3.49 and 3.54 (3H, 2xs); 3.72-3.86 (2H, 2xAB, J=14.4,14.4); 5.05 (1H, m); 6.00 (1H, m); 6.34-7.72 (13H, m); IR (film): 3278, 2969, 1648, 1507, 1455cm^{-1}; MS(ES^+): 455(M+H) Analysis calculated for $C_{28}H_{30}N_4O_4$; C, 73.98; H, 6.65; N,12.32%. Found: C, 73.69; H, 6.44; N, 12.12%.

EXAMPLE 3.

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-4-yl-ethyl)-propionamide, [R-(R*,S*)]

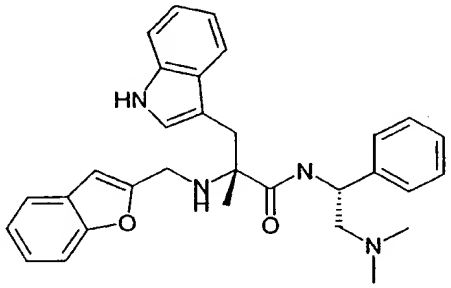


Intermediate I (0.174g, 0.5mmol), HBTU (0.190g, 0.5mmol), DIPEA (0.348mL, 2mmol) and the amine (prepared as described in US 5594022) (252mg, 0.6mmol) were stirred in DMF (25mL) for 18 h. The reaction mixture was evaporated and the residue taken up in EtOAc and washed with 10%Na_2CO_3, and brine. Drying and purification by column chromatography using 3%MeOH/DCM gave a white solid (0.14g, 62%). mp=66-69°C; NMR ($CDCl_3$): δ

1.44(3H,d, J= 7.2Hz); 1.50 (3H, s); 1.96 (1H, bs) 3.12 (1H, d, J=14.4Hz) and 3.23 (1H, d, J=14.4Hz); 3.80 (1H, d, J=14.2Hz) and 3.92(1H, d, J=14.2Hz); 5.02 (1H, m); 6.48 (1H, s); 6.89-8.00 (12H, m); 8.03 (1H, s); 8.46(2H, m); IR (film) 3326, 2978, 1660, 1602, 1505, 1455cm^{-1}; MS(ES$^+$) 453 (M+1); $[\alpha]_D^{23}$= -29.0° (c=0.39, MeOH); Analysis calculated for $C_{28}H_{28}N_4O_2$. 0.2H_2O: C, 73.73; H, 6.28; N, 12.28% Found: C, 73.76; H, 6.25; N, 12.08%.

EXAMPLE 4

2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-dimethylamino-1-phenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide, (R,R)



Step 1

To a solution of (R)-2-phenyl glycinol (2.11g, 15mmol) and benzyl chloroformate (2.35mL, 16.5mmol) in THF (30mL) at 0°C was added triethylamine (2.30mL, 16.5mmol) in THF (5mL). After stirring for 18 h at room temperature, the mixture was filtered and evaporated to a white solid which was purified by column chromatography on silica using 50% EtOAc/ heptane, giving a white solid (4.00g, 98%); NMR ($CDCl_3$): δ 3.88 (2H, m); 4.85 (1H, m); 5.10 (2H, m); 5.48 (1H, m); 7.23-7.40 (10H, m); IR (film): 3324, 2950, 1687, 1540, 1259cm^{-1};

Step 2

To a solution of the alcohol from step one (1.00g, 3.68mmol) and triethylamine (1.16mL, 8mmol) in THF (20mL) was added a solution of methane sulphonylchloride (0.31mL, 4.0mmol) in THF (3mL). The mixture was stirred for 1 h. 2M dimethylamine in THF solution. (17mL, 34mmol) was added and the sealed mixture was stirred for 12 days. Evaporation of the solvent and purification by column chromatography using 2% MeOH/DCM gave a yellow oil (0.399g, 36%); NMR ($CDCl_3$): δ 2.23 (6H, s); 2.35-2.58 (2H, m); 4.64 (1H, bs); 5.06 (2H, m); 5.77 (1H, bs); 7.20-7.40 (10H, m); IR (film): 3330, 2945, 1716, 1538, 1246, 1050cm^{-1}.

Step 3 Intermediate IV

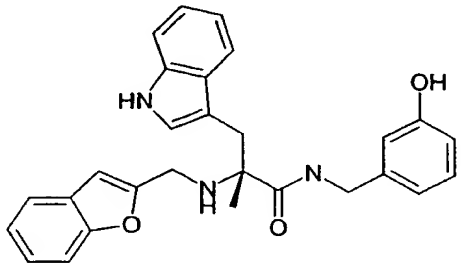
The protected amine from step one (0.226g, 0.75mmol) was dissolved in methanol (30mL) and Pearlman's catalyst (30mg) was added. The mixture was shaken for 2 h at 50 psi and then filtered through kieselguhr. Evaporation gave a yellow syrup (0.127g, 100%); NMR ($CDCl_3$): δ 2.22-2.51 (8H, m); 4.07 (1H, m); 7.22-7.39 (5H, m).

Step 4

Intermediate I (0.174g, 0.5mmol), HBTU (0.19g, 0.5mmol), DIPEA (0.174mL, 1.0mmol) and the amine (Intermediate IV) (0.12mg, 0.73mmol) were stirred in DMF (15mL) for 18 h. The reaction mixture was evaporated and the residue taken up in EtOAc and washed with 10%Na_2CO_3, and brine. Drying and purification by column chromatography using 1% MeOH/DCM and reverse phase chromatography using 40-100% MeOH/H_2O gave a white solid (0.10g, 40%). mp=130-134°C; NMR ($CDCl_3$) δ 1.44 (3H, s); 2.16 (6H, s); 2.41 (1H, dd, J=5.6, 12.4Hz) and 2.59 (1H, dd, H=10.0, 12.4); 3.17 (2H, s); 3.86 (1H, d, 14.4Hz) and 3.92 (1H, d, J=14.6Hz); 4.95 (1H, m); 6.55 (1H, s); 6.90 (1H, s); 7.09-7.67 (13H, m); 8.01 (1H, s); 8.18, d, J=6.6Hz); IR (film) 3317, 2934, 1658, 1496, 1455cm^{-1}; MS(ES^+) 482 (M+1); $[\alpha]_D^{23}$=31.9 (c=0.72, MeOH); Analysis calculated for $C_{31}H_{34}N_4O_2$: C, 75.28; H, 6.93; N, 11.33% Found: C, 75.24; H, 6.92; N, 11.15%.

EXAMPLE 5.

2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-hydroxy-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide, R



Step 1

Intermediate I (0.348g, 1mmol), HBTU (0.379g, 1mmol), DIPEA (0.35mL, 2mmol) and 3-methoxybenzylamine (0.206g, 1.5mmol) were stirred in DMF (17mL) for 18 h. The reaction mixture was evaporated and the residue taken up in EtOAc and washed with 10%Na_2CO_3, and brine. Drying and purification by column chromatography using 40% EtOAc/Heptane gave a white solid (0.190g; 41%). mp=42-47°C; NMR ($CDCl_3$): δ 1.50 (3H, s); 1.90 (1H, bs); 3.20

(1H, d, J= 14.4Hz) and 3.28 (1H, d, J= 14.4Hz); 3.72-3.82 (4H, m); 3.88 (1H, d, J=14.0Hz); 4.37 (2H, d, J=6.0Hz); 6.37 (1H, s); 6.75-7.70 (14H, m); 8.12 (1H, s); IR (film): 3322, 2920, 1654, 1602, 1455, 1256cm^{-1}; MS(ES$^+$) 468 (M+1); $[\alpha]_D^{23.5}$ = -31.3° (c=1.01, MeOH); Analysis calculated for $C_{29}H_{29}N_3O_3$: C, 74.50; H, 6.25; N, 8.99%; Found: C, 74.20; H, 6.24; N, 8.78%

Step 2

1.0M Boron tribromide in dichloromethane (0.62mL; 0.62mmol) was added dropwise to a solution of the methoxy compound from step one (0.146g; 0.31mmol) in dichloromethane at -70°C under N_2, warmed slowly to room temperature and stirred for 18 h. The mixture was poured onto 10g crushed ice/ 2M HCl (15mL) and stirred for 10 min. Neutralizing with Na_2CO_3, extraction with EtOAc and purification by column chromatography using 40% EtOAc/ heptane gave a white solid (0.115g; 82%). mp=60-69°C; NMR ($CDCl_3$): δ1.53 (3H, s); 1.96 (1H, bs); 3.14 (1H, d, J= 14.4Hz) and 3.37 (1H, d, J=14.4Hz); 3.81 (1H, d, J=14.0Hz) and 3.93 (1H, d, J=14.0Hz); 4.14-4.50 (2H, m); 5.23 (1H, bs); 6.32-7.82 (15H, m); 8.14 (1H, s); IR (film): 3333, 2907, 1645, 1599, 1520, 1455, 1254cm^{-1}; MS(ES$^+$): 454 (M+1); $[\alpha]_D^{23.5}$ = -25.9° (c=0.73, MeOH); Analysis calculated for $C_{28}H_{27}N_3O_3$. 0.5 H_2O: C, 72.71; H, 6.10; N, 9.08% Found: C, 72.83, 72.86; H, 6.03, 5.96; N, 8.81, 8.83%.

Scheme 6 describes the synthesis of intermediate V, which is required for Examples 6 to 17.

Boc-tryptophan was coupled to alpha-methylbenzylamine using HBTU activation. The Boc group was removed using formic acid in DCM to give Intermediate V.

Examples 6, 8 and 10 to 21 were prepared by a reductive amination of the relative aldehydes and Intermediate V with sodium triacetoxyborohydride as shown in scheme 7.

Scheme 8 outlines the synthesis of Example 7. 2-Benzofuranacetic acid was reacted with ethyl chloroformate in THF and then reduced with lithium borohydride. The alcohol was then converted to the corresponding mesylate and reacted with Intermediate V to give Example7.

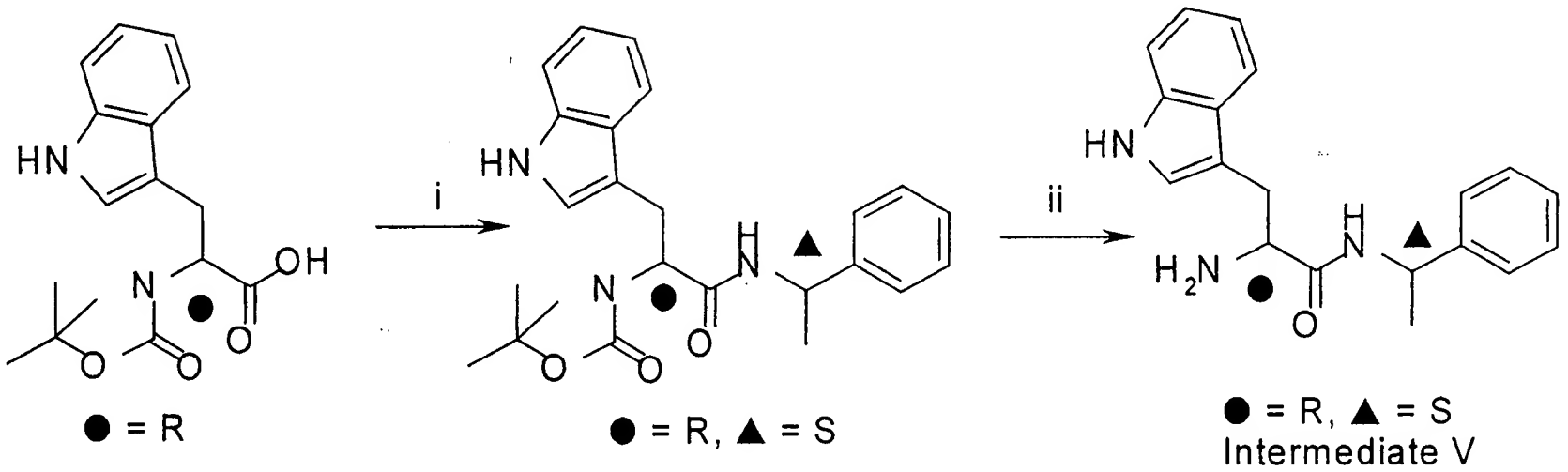
Scheme 9 describes the synthesis of Example 9. 2-Hydroxymethyl benzimidazole was reacted with bis(4-nitrophenyl) carbonate in DMF to form the cyclic carbamate. This compound was then reacted with intermediate V to give Example 9.

The synthesis of Intermediate VI is shown in scheme 10; the intermediate was used to prepare Example 10. Benzo[b]thiophene-2-carboxylic acid was activated with ethyl chloroformate and then coupled with *N,O*-dimethylhydroxylamine. The Weinreb amide was then reduced to the corresponding aldehyde with DIBAL.

The synthesis of Example 22 is described in scheme 11. 2-benzofurancarboxaldehyde was reacted with hydroxylamine in aqueous potassium hydroxide/EtOH. The oxime was then reduced with lithium aluminum hydride to give the amine. The corresponding isocyanate, prepared by reacting the amine with triphosgene in DCM/pyridine, was reacted with 2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide to give Example 22.

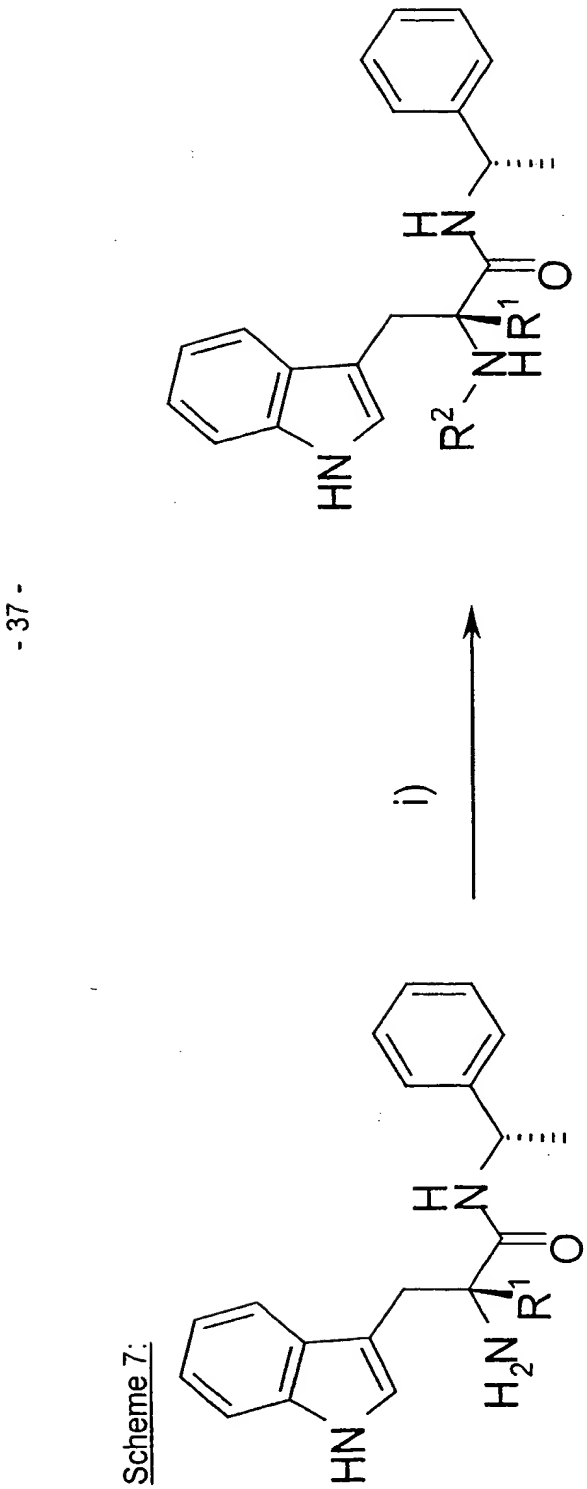
Scheme 12 shows the synthesis of the key intermediate VII that was used in the synthesis of Examples 192 to 308. This N-carboxyanhydride was prepared by reacting intermediate I with phosgene in toluene.

Scheme 6:



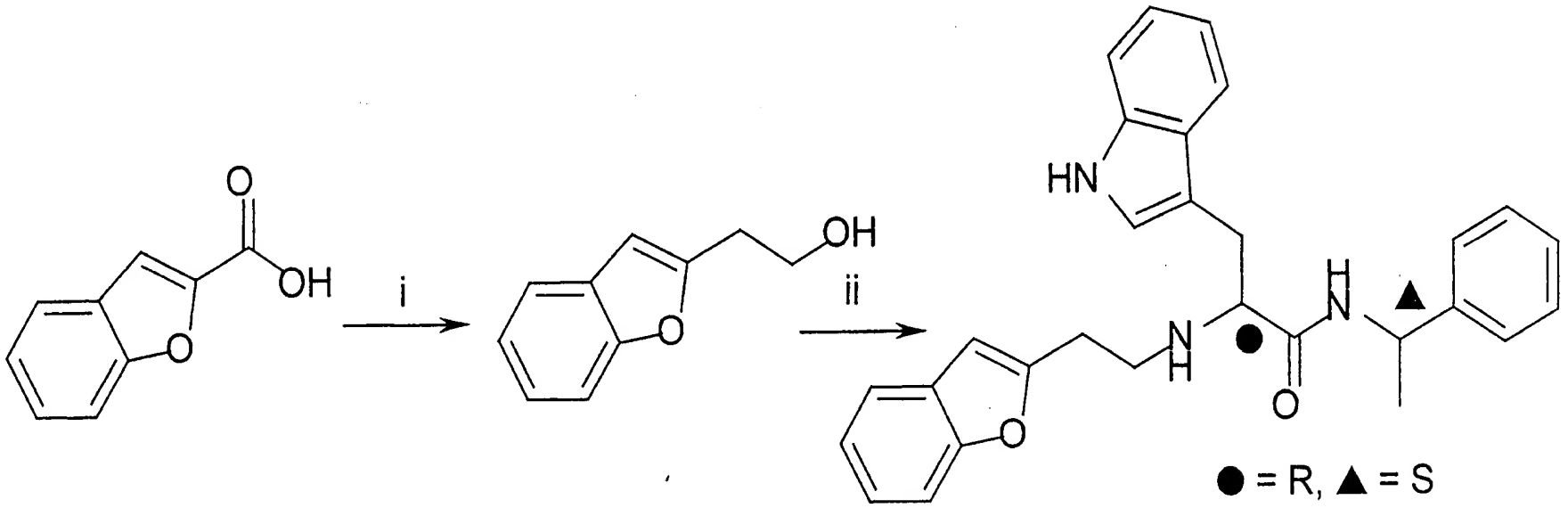
i. HBTU,DMF, DIPEA, α-methylbenzylamine

ii. Formic acid, DCM



Example	R^1	R^2
6	H	2-Benzofuran-CH_2
8	H	2-(4,5-Dimethylfuran)-CH_2
10	H	2-Benzothiophene-CH_2
11	H	3-quinoline-CH_2
12	H	2-(5-Cl-thiophene)-CH_2
13	H	(3-SCF_3-Ph)-CH_2
14	H	(3-CN-Ph)-CH_2
15	H	(3-NO_2-Ph)-CH_2
16	H	(3-OCF_3-Ph)-CH_2
17	H	(3-OH-Ph)-CH_2
18	CH_3	2-Benzofuran-CH_2
19	CH_3	3-Benzofuran-CH_2
20	CH_3	2-pyrrole-CH_2
21	CH_3	3-pyrazole-CH_2

Scheme 8:



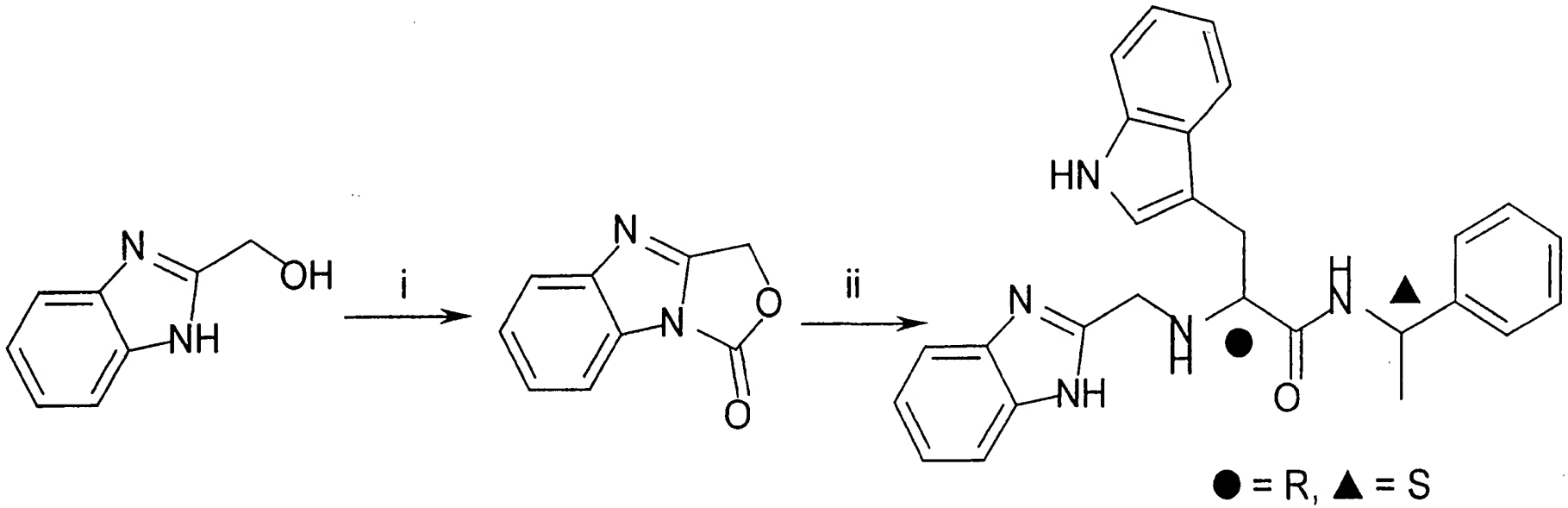
Example 7

i. a) NMM, EtOCOCl, THF b) $LiBH_4$

ii. Ether, CH_3SO_2Cl, NEt_3, Intermediate V

- 39 -

Scheme 9:

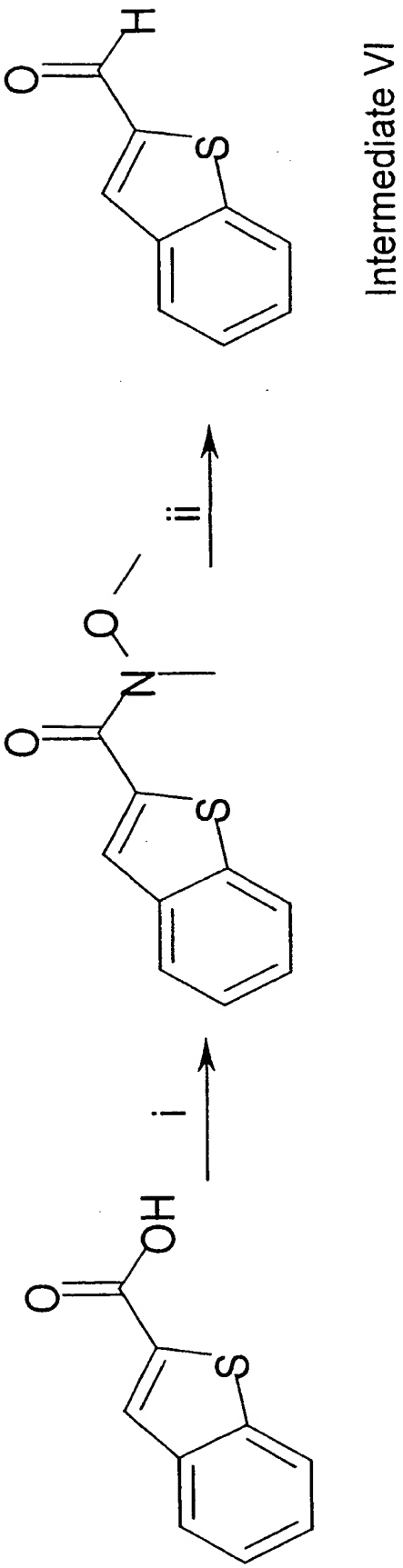


Example 9

i. bis(4-nitrophenyl) carbonate, DMF

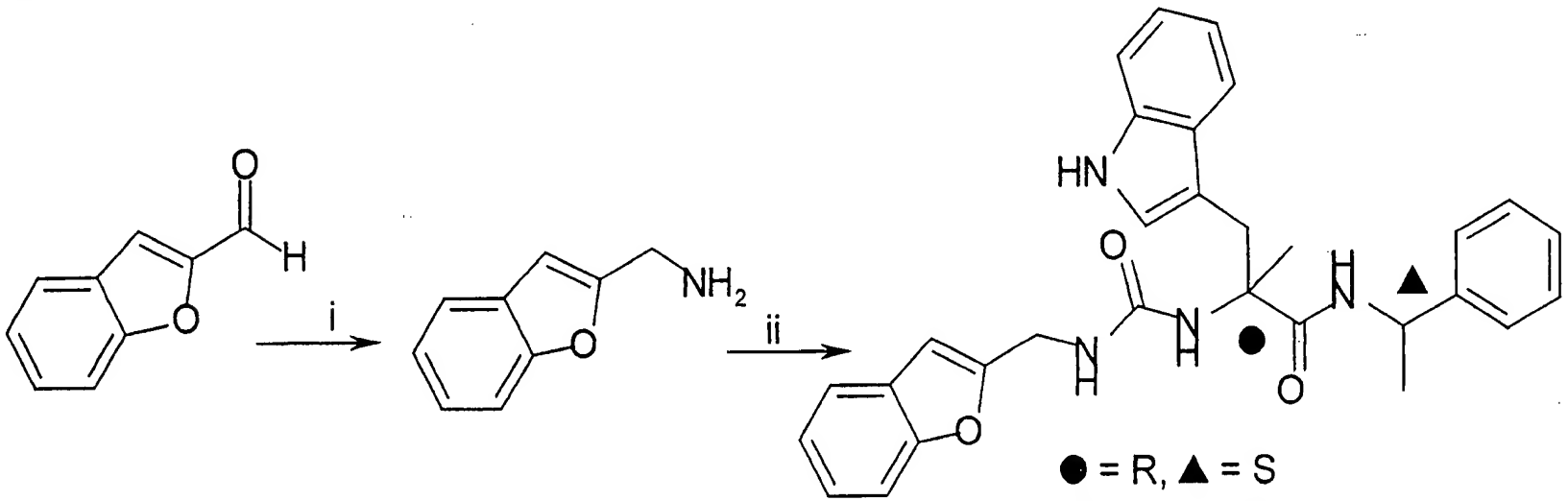
ii. Intermediate V, DMF

- 40 -



Scheme 10:

Scheme 11



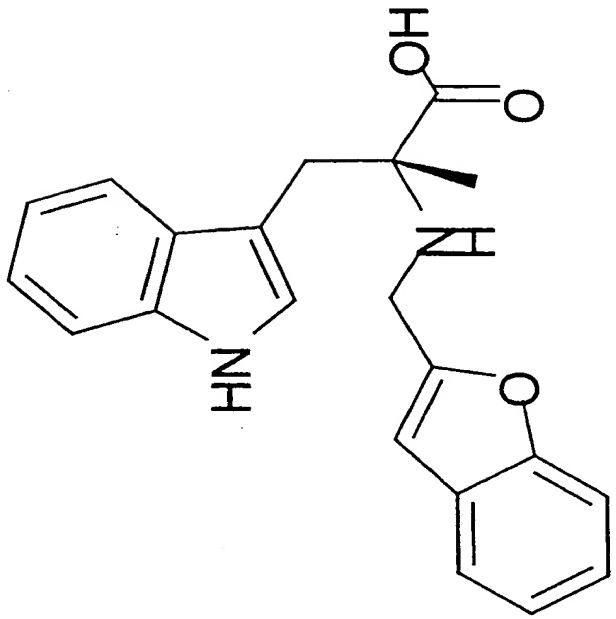
Example 22

i. a) KOH, NH_2OH, EtOH, H_2O

b) $LiAlH_4$

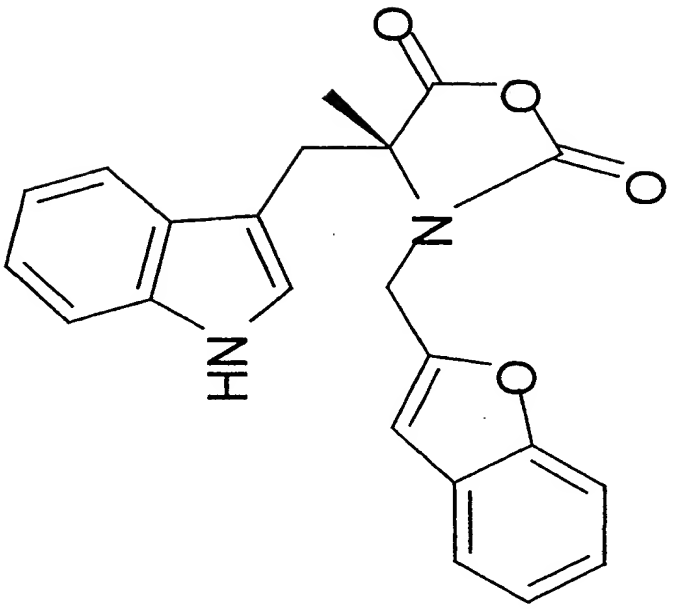
ii. triphosgene, DCM, pyridine,
2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide

Scheme 12:



i Phosgene, toluene

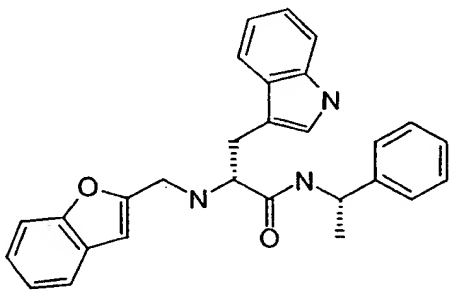
i



Intermediate VII

EXAMPLE 6.

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



Step 1. Intermediate V

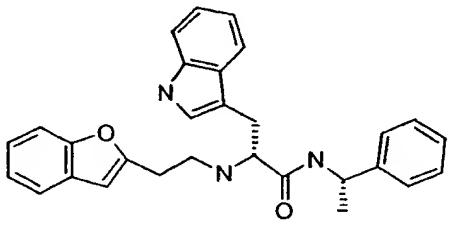
To a stirred solution of Boc-(R)-Trp-OH (6.08g, 0.02mol) in DMF (50mL) was added HBTU (7.59, 0.02mol) and DIPEA (3.57mL, 0.02mol). After 5 min DIPEA (3.57mL, 0.02mol) and (S)-(-)-α-methylbenzylamine in DMF (10mL) was added. After a further 60 min, the solvent was removed under reduced pressure. The residue was taken up in EtOAc (250mL) and washed with brine (50mL), 1N HCl (100mL), saturated $NaHCO_3$ (3 x 100mL), brine (50mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20mL) and formic acid (30mL). The reaction was stirred over night at room temperature before refluxing for 4 h. The solvent was removed under reduced pressure and the product was crystallized from ether. Stirring in EtOAc (100mL) for 4 h and filtration gave pure product (4.17g, 68%). The filtrate was purified by chromatography using EtOAc and then EtOAc/MeOH/NH_3(aq) (95:5:0.5) as eluent. Crystallization from ether gave white crystalline solid (0.98g , 16%); mp 142-144°C; $[\alpha_D{}^{19}$=-83.9° (*c*=1, MeOH); IR (film): 3338, 3295, 3059, 2975, 2928, 1649, 1518, 1494, 1455, 1342, 1104, 894, 740 cm^{-1}; NMR ($CDCl_3$): δ 1.44 (3H, d, J=7.1 Hz); 1.51 (2H, s); 2.95 (1H, d.d, J=14.4 and 8.5 Hz); 3.36 (1H, d.d, J=14.4 and 4.4 Hz); 3.74 (1H, d.d, J=8.5 and 4.4 Hz); 5.05-5.15 (1H, m); 6.95 (1H, d, J=2.2 Hz); 7.10-7.38 (8H, m); 7.48-7.52 (1H, m); 7.66-7.69 (1H, m); 7.98 (1H, s); MS m/e (APCI$^+$): 309.1 (20%), 308.1 (100%, M^+ + H); Analysis calculated for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.66%. Found: C, 74.07; H, 6.87; N, 13.70%.

Step 2.

To a stirred solution of 2-benzofurancarboxaldehyde (0.73g, 5mmol) in 1,2-dichloroethane (20mL) was added intermediate V (1.54g, 5mmol) followed by sodium triacetoxyborohydride (1.48g, 7mmol). After stirring for 3 h the reaction was cautiously quenched with saturated $NaHCO_3$ (20mL) and extracted with CH_2Cl_2 (3x 50mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography using 30% EtOAc in heptane as eluent to give pure product as a glass (2.0g, 91%); $[\alpha_D]^{20}$=+34.0° (*c*=0.5, MeOH); IR (film): 3316, 3059, 2973, 2925, 1653, 1517, 1455, 1341, 1254, 1104, 1010, 909, 741 cm^{-1}; NMR ($CDCl_3$): δ 1.38 (3H, d, J=7.1 Hz); 1.93 (1H, s); 2.92 (1H, d.d, J=14.6 and 9.3 Hz); 3.29-3.35 (1H, m); 3.58 (1H, d.d, J=9.3 and 4.2 Hz); 3.75 (1H, d, J=14.9 Hz); 3.82 (1H, d, J=14.9 Hz); 5.07-5.15 (1H, m); 6.36 (1H, s); 6.87 (1H, d, J=2.2 Hz); 7.04-7.08 (1H, m); 7.15-7.35 (10H, m); 7.43-7.45 (1H, m); 7.58-7.64 (2H, m); 7.92 (1H, s); MS m/e (APCI$^+$): 439.9 (5%), 438.9 (34%), 437.9 (100%, M^+ + H), 307.0 (9%); Analysis calculated for $C_{28}H_{27}N_3O_2$: C, 76.86; H, 6.22; N, 9.60%. Found: C, 77.11; H, 6.31; N, 9.67%.

EXAMPLE 7.

2-(2-Benzofuran-2-yl-ethylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



Step 1

A solution of N-methylmorpholine (NMM, 5.31g, 52.5mmol) in THF (30mL) was added dropwise over 15 min to a stirred solution of 2-benzofuranacetic acid (8.80g, 50mmol) and ethyl chloroformate (5.70g, 52.5mmol) in THF (150mL, anhydrous) at 0°C. The reaction mixture was stirred for 1 h at room temperature before filtering off the precipitate of NMM.HCl. The filtrate was cooled to 0°C and a solution of lithium borohydride (30mL, 60mmol, 2M in THF) was added dropwise over 30 min. The reaction was allowed to reach room temperature and stirred over night before being cautiously quenched with 1N HCl (100mL) -vigorous effervescence. The THF was removed under reduced pressure and the

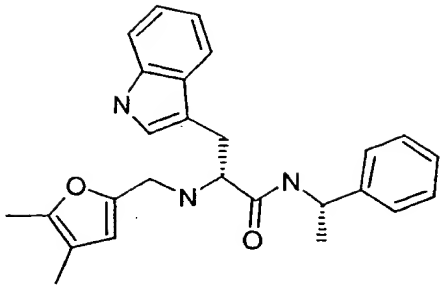
aqueous phase was extracted with EtOAc (200mL). The organic phase was washed with 1N HCl, H_2O, saturated $NaHCO_3$ (x2), brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure gave intermediate VI (7.74g, 93%). Used in the next step without further purification. IR (film): 3347, 2957, 2887, 1603, 1587, 1455, 1422, 1317, 1252, 1167, 1105, 1049, 945, 926, 881, 854, 807, 751 cm^{-1}; NMR ($CDCl_3$): δ 1.64 (1H, t, J=6.0 Hz); 3.05 (2H, t, J=6.2 Hz); 4.00 (2H, q, J=6.1 Hz);.6.51 (1H, d, J=1.0 Hz); 7.17-7.25 (2H, m); 7.41-7.44 (1H, m); 7.49-7.52 (1H, m).

Step2

To an ice-cold solution of alcohol VI (1.62g, 10mmol) and NEt_3 (1.01g, 10mmol) in ether (50mL, anhydrous) was added a solution of methanesulphonyl chloride (1.20g, 10.5mmol) dropwise over 5 min. The ice bath was removed and the reaction was stirred at room temperature for 30 min before filtering off the NEt_3.HCl. The ether was removed under reduced pressure. To a portion of the mesylate (240mg, 1mmol) dissolved in toluene (50mL, anhydrous) was added amine V. The reaction was refluxed for 48 h, a further equivalent of NEt_3 was added, and reflux was continued for a further 48 h. The reaction mixture was cooled and washed with 1N NaOH, the organic layer was dried ($MgSO_4$), and solvent removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 20% EtOAc in heptane as eluent and then on reverse phase silica using 70% MeOH in H_2O as elan. Product crystallized on drying in vacuum oven to give pure product (82mg, 18%); mp 105-107°C; $[\alpha]_D^{22}$=-1.2° (*c*=0.25, MeOH); IR (film): 3305, 3058, 2924, 2851, 1651, 1515, 1455, 1356, 1342, 1252, 1166, 1105, 742 cm^{-1}; NMR ($CDCl_3$): δ 1.37 (3H, d, J=7.1 Hz); 1.57 (1H, s); 2.72-2.97 (5H, m); 3.28-3.34 (1H, m); 3.44-3.48 (1H, m); 5.07-5.15 (1H, m); 6.06 (1H, s); 6.75 (1H, d, J=2.2 Hz); 7.06-7.33 (11H, m); 7.40-7.44 (1H, m); 7.51 (1H, d, J=8.5 Hz); 7.62-7.65 (2H, m); MS m/e (ES^+): 453.1 (33%), 452.2 (100%, M^+ + H); Analysis calculated for $C_{29}H_{29}N_3O_2$: C, 77.14; H, 6.47; N, 9.31%. Found: C, 77.06; H, 6.48; N, 9.30%.

EXAMPLE 8.

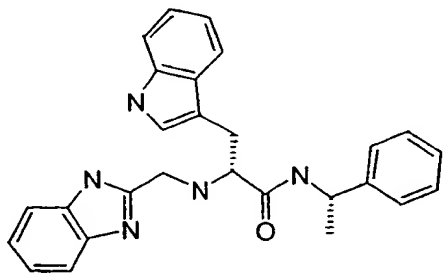
2-[(4,5-Dimethyl-furan-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



To a stirred solution of the 4,5-dimethyl-2-furaldehyde (124mg, 1mmol) in 1,2-dichloroethane (20mL) was added intermediate V (307mg, 1mmol) followed by sodium triacetoxyborohydride (424mg, 2mmol). After stirring over night the reaction was cautiously quenched with saturated $NaHCO_3$ (20mL) and extracted with CH_2Cl_2 (2 x 20mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 25% EtOAc in heptane as eluent to give pure product as a glass (196mg, 47%); $[\alpha]_D^{21}$=+18.6° (*c*=0.5, MeOH); IR (film): 3312, 3059, 2971, 2922, 1651, 1516, 1455, 1342, 1220, 1106, 741 cm^{-1}; NMR ($CDCl_3$): δ 1.44 (3H, d, J=6.8 Hz); 1.60-1.90 (1H, br.s); 1.83 and 2.06 (each 3H, s); 2.89 (1H, d.d, J=14.6 and 9.3 Hz); 3.26-3.32 (1H, m); 3.49 (1H, d, J=14.4 Hz); 3.50-3.54 (1H, m); 3.58(1H, d, J=14.4 Hz); 5.08-5.16 (1H, m); 5.76 (1H, s); 6.89 (1H, d, J=2.2 Hz); 7.01-7.11 (1H, m); 7.17-7.36 (7H, m); 7.62-7.65 (2H, m); 7.95 (1H, s); MS m/e (ES^+): 417.3 (31%), 416.3 (100%, M^+ + H), 308.3 (34%); Analysis calculated for $C_{26}H_{29}N_3O_2.0.2H_2O$: C, 74.51; H, 7.07; N, 10.03%. Found: C, 74.43; H, 6.82; N, 10.03%.

EXAMPLE 9.

2-[(1H-Benzoimidazol-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



Step 1

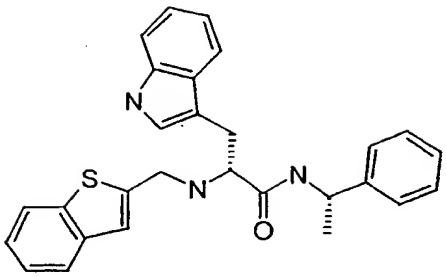
A solution of 2-hydroxymethyl benzimidazole (1.19g, 8mmol) and bis(4-nitrophenyl) carbonate (2.43g, 8mmol) in DMF (20mL, anhydrous) was stirred for 12 h at room temperature. The DMF was removed under reduced pressure and the residue stirred in ether (50mL) for 2 h. Filtration and washing with ether (50mL) gave crystalline intermediate VII (1.04g, 74%); IR (film): 1819, 1623, 1592, 1568, 1486, 1445, 1411, 1369, 1359, 1147, 1106, 1076, 1009, 997, 941, 862, 847, 765, 750, 741 cm^{-1}; NMR ($CDCl_3$): δ 5.49 (2H, s); 7.42-7.50 (2H, m); 7.79-7.84 (1H, m); 7.88-7.93 (1H, m).

Step2

The product from step 1 (174mg, 1mmol) and intermediate V (307mg, 1mmol) were dissolved in DMF (10mL, anhydrous) and stirred at 60°C for 10 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on reverse phase silica using 60% MeOH in H_2O as eluent. The solvent was removed under reduced pressure and the residue was crystallized from EtOAc to give pure product (396mg, 91%); mp 148-152.5°C; $[\alpha]_D^{21}$=+24.2° (*c*=0.5, MeOH); IR (film): 3300, 3058, 2923, 1651, 1520, 1455, 1340, 1271, 1235, 1218, 1109, 1013, 909, 739 cm^{-1}; NMR ($CDCl_3$): δ 1.31 (3H, d, J=7.1 Hz); 2.00-2.50 (1H, br.s); 3.04 (1H, d.d, J=14.4 and 8.8 Hz); 3.29 (1H, d.d, J=14.4 and 5.2 Hz); 3.50 (1H, d.d, J=8.8 and 5.2 Hz); 3.94 (1H, d, J=15.9 Hz); 4.04 (1H, d, J=15.9 Hz); 5.03-5.10 (1H, m); 6.85 (1H, d, J=7.8 Hz); 6.99 (1H, d, J=2.2 Hz); 7.10-7.30 (10H, m); 7.20-7.70 (1H, br.s); 7.42 (1H, d, J=8.1 Hz); 7.66 (1H, d, J=7.8 Hz); 8.06 (1H, s); 8.80-9.20 (1H, br.s); MS m/e (ES^+): 439.3 (28%), 438.3 (100%, M^+ + H); Analysis calculated for $C_{27}H_{27}N_5O$: C, 74.12; H, 6.22; N, 16.01%. Found: C, 74.04; H, 6.19; N, 15.95%.

EXAMPLE 10

2-[(Benzo[b]thiophen-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide



Step 1

A solution of NMM (2.309mL, 21mmol) in THF (10mL) was added dropwise to a stirred ice cooled solution of benzo[b]thiophene-2-carboxylic acid (3.56g, 20mmol) and ethyl chloroformate (2.008mL, 21mmol) in THF (150mL) over 15mins. The reaction mixture was stirred at room temperature for 1 h before adding *N,O*-dimethylhydroxylamine hydrochloride (2.146g, 22mmol) and NMM (2.419mL, 22mmol). The reaction was stirred at room temperature over night. The solvent was removed under reduced pressure. The residue was taken up in EtOAc (100mL) and washed with 2N HCl (3 x 100mL), 2N NaOH (100mL), H_2O, brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 30% EtOAc in heptane as eluent. Crystallization from ether/heptane gave pure product (3.24g, 73%).

To a stirred solution of the Weinreb amide (2.06g, 9.3mmol) in THF (100mL, anhydrous) under nitrogen at 0°C was added diisobutylaluminum hydride (11mL, 11mmol, 1M in CH_2Cl_2) dropwise. After 20 min the reaction mixture was poured onto ice cold 2N HCl and extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 5% EtOAc in heptane as eluent to give solid benzo[b]thiophene-2-carboxaldehyde (Intermediate VI) (665mg, 44%). IR (film): 1669, 1592, 1516, 1431, 1255, 1224, 1135, 840, 747, 725 cm^{-1}; NMR ($CDCl_3$): δ 7.42-7.54 (2H, m); 7.91 (1H, d, J=8.1 Hz); 7.95(1H, d, J=7.8 Hz); 8.04 (1H, s); 10.12 (1H, s).

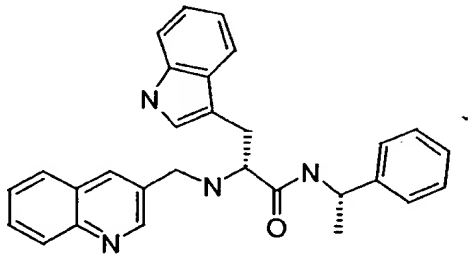
Step 2

To a stirred solution of the benzo[b]thiophene-2-carboxaldehyde (Intermediate VI) (162mg, 1mmol) in 1,2-dichloroethane (20mL) was added intermediate V (307mg, 1mmol) followed by sodium triacetoxyborohydride (424mg, 2mmol). After stirring over night the reaction was cautiously quenched with saturated $NaHCO_3$ (20mL) and extracted with CH_2Cl_2 (2 x 20mL).

The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 20% EtOAc in heptane as eluent. Crystallization from ether/heptane gave pure product (305mg, 67%); mp 102-108 °C; $[\alpha]_D^{21}$=+51.4° (*c*=0.5, MeOH); IR (film): 3311, 3059, 2925, 1651, 1515, 1456, 743 cm^{-1}; NMR ($CDCl_3$): δ 1.40 (3H, d, J=7.1 Hz); 1.97 (1H, s); 2.99 (1H, d.d, J=14.7 and 8.8 Hz); 3.35 (1H, d.d, J=14.4 and 4.2 Hz); 3.59 (1H, d.d, J=8.5 and 4.4 Hz); 3.94 (2H, m); 5.07-5.16 (1H, m); 6.91-6.93 (2H, m); 7.06-7.11 (1H, m); 7.17-7.37 (9H, m); 7.50 (1H, d, J=8.5 Hz); 7.60 (1H, d.d, J=7.0 and 1.6 Hz); 7.65 (1H, d, J=8.1 Hz); 7.72-7.76 (1H, m); 7.95 (1H, s); MS m/e (ES^+): 476.1 (60%, M^+ + Na), 454.1 (100%, M^+ + H), 402.2 (25%); (ES^-): 453.2 (25%), 452.1 (100%, M^- - H); Analysis calculated for $C_{28}H_{27}N_3OS$: C, 74.14; H, 6.00; N, 9.26; S, 7.07%. Found: C, 74.27; H, 6.16; N, 9.31; S, 7.11%.

EXAMPLE 11.

3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[(quinolin-3-ylmethyl)-amino]-propionamide, [R-(R*,S*)]

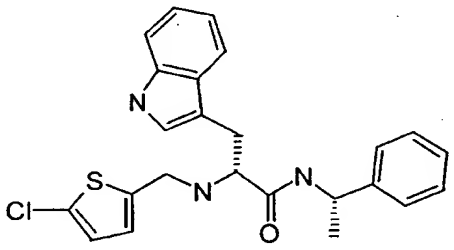


Method as for Example 10, step 2. The residue was purified by chromatography on normal phase silica using 2% MeOH in CH_2Cl_2 as eluent. Crystallization from EtOAc/heptane gave pure product (340mg, 76%); mp 161-163°C; $[\alpha]_D^{22}$=+40° (*c*=0.5, MeOH); IR (film): 3280, 3055, 2972, 2926, 1655, 1515, 1497, 1456, 1342, 1127, 742 cm^{-1}; NMR ($CDCl_3$): δ 1.40 (3H, d, J=7.1 Hz); 1.90 (1H, s); 2.96 (1H, d.d, J=14.7 and 9.0 Hz); 3.36 (1H, d.d, J=14.5 and 4.5 Hz); 3.53-3.56 (1H, m); 3.78 (1H, d, J=13.7 Hz); 3.92 (1H, d, J=13.7 Hz); 5.08-5.16 (1H, m); 6.90 (1H, d, J=2.2 Hz); 7.03-7.08 (1H, m); 7.15-7.20 (1H, m); 7.23-7.37 (6H, m); 7.43 (1H,d J=8.3 Hz); 7.49-7.51 (1H, m); 7.59-7.72 (4H, m); 8.02 (1H, s); 8.04 (1H, d, J=8.3 Hz); 8.66 (1H, d, J=2.2 Hz); MS m/e (ES^+): 471.1 (31%, M^+ + Na), 449.1 (100%, M^+ + H); Analysis

calculated for $C_{29}H_{28}N_4O$: C, 77.65; H, 6.29; N, 12.49%. Found: C, 78.02; H, 6.30; N, 12.48%.

EXAMPLE 12

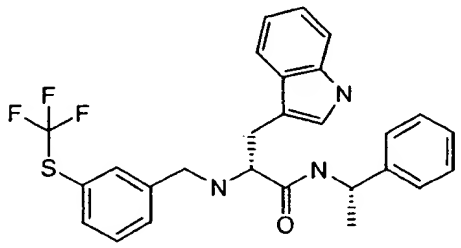
2-[(5-Chloro-thiophen-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



Method as for Example 10, step 2. The residue was dissolved in aqueous acetonitrile and acidified using formic acid before being purified by chromatography on reverse phase silica using 40% CH_3CN in H_2O (0.1% formic acid in mobile phases) as eluent. The solvent was removed under reduced pressure and the residue was suspended between EtOAc and saturated $NaHCO_3$. The EtOAc was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give pure product as a glass (245mg, 56%); $[\alpha]_D^{22}$=+26.2° (*c*=0.5, MeOH); IR (film): 3307, 3059, 2973, 2925, 1652, 1515, 1455, 1342, 1230, 1105, 1061, 1000, 796, 742 cm^{-1}; NMR ($CDCl_3$): δ 1.43 (3H, d, J=6.8 Hz); 1.85 (1H, s); 2.96 (1H, d.d, J=14.7 and 8.5 Hz); 3.31 (1H, d.d, J=14.5 and 4.5 Hz); 3.49-3.53 (1H, m); 3.71-3.79 (2H, m); 5.07-5.15 (1H, m); 6.50 (1H, d, J=3.7 Hz); 6.65 (1H, d, J=3.9 Hz); 6.91 (1H, d, J=2.4 Hz); 7.09-7.14 (1H, m); 7.18-7.39 (8H, m); 7.63 (1H, d, J=7.6 Hz); 7.98 (1H, s); MS m/e (ES^+): 437.9 (100%, M^+ + H); Analysis calculated for $C_{24}H_{24}N_3OSCl$: C, 65.81; H, 5.52; N, 9.59; Cl, 8.09; S, 7.32%. Found: C, 65.54; H, 5.45; N, 9.40; Cl, 7.85; S, 7.42%.

EXAMPLE 13.

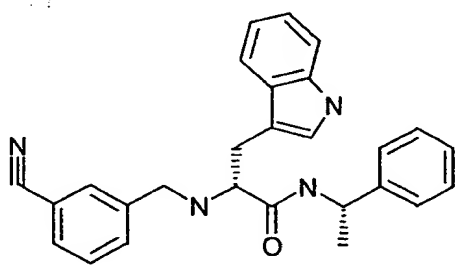
3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-(3-trifluoromethylsulfanyl-benzylamino)-propionamide, [R-(R*,S*)]



To a stirred solution of 3-(trifluoromethylthio)benzaldehyde (72mg, 0.55mmol) in 1,2-dichloroethane (20mL) was added intermediate V (154mg, 0.5mmol) followed by sodium triacetoxyborohydride (148mg, 0.7mmol). After stirring over night the reaction was cautiously quenched with saturated $NaHCO_3$ (20mL) and extracted with CH_2Cl_2 (3 x 50mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 30% EtOAc in heptane as eluent. The solvent was removed under reduced pressure to give pure product as a glass (193mg, 77%); IR (film): 3306, 3058, 2972, 2923, 1651, 1516, 1456, 1342, 1114, 743 cm^{-1}; NMR ($CDCl_3$): δ 1.41 (3H, d, J=6.8 Hz); 1.60-1.90 (1H, br.s); 2.96 (1H, d.d, J=14.5 and 8.9 Hz); 3.32 (1H, d.d, J=14.4 and 4.4 Hz); 3.48 (1H, d.d, J=8.9 and 4.5 Hz); 3.62 (1H, d, J=13.9 Hz); 3.76 (1H, d, J=13.7 Hz); 5.08-5.16 (1H, m); 6.91 (1H, d, J=2.2 Hz); 7.07-7.48 (13H, m); 7.60 (1H, d, J=7.8 Hz); 7.97 (1H, s); MS m/e (ES^+): 499.4 (32%), 498.4 (100%, $M^+ + H$); Analysis calculated for $C_{27}H_{26}N_3OSF_3.0.25H_2O$: C, 64.59; H, 5.32; N, 8.37; S, 6.39%. Found: C, 64.69; H, 5.34; N, 8.30; S, 6.27%.

EXAMPLE 14.

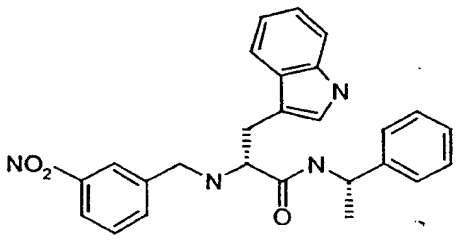
2-(3-Cyano-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



Method as for Example 13. Chromatography on normal phase silica using 45% EtOAc in heptane as the eluent and subsequent removal of the solvent under reduced pressure gave pure product as a glass (130mg, 62%); IR (film): 3312, 3059, 2973, 2924, 2229, 1652, 1516, 1456, 1342, 1231, 1101, 743 cm^{-1}; NMR ($CDCl_3$): δ 1.42 (3H, d, J=6.8 Hz); 1.87 (1H, s); 2.91 (1H, d.d, J=14.5 and 9.2 Hz); 3.32 (1H, d.d, J=14.5 and 4.0 Hz); 3.41 (1H, d.d, J=9.0 and 4.4 Hz); 3.58 (1H, d, J=14.2 Hz); 3.76 (1H, d, J=14.2 Hz); 5.08-5.17 (1H, m); 6.94 (1H, d, J=2.2 Hz); 7.07-7.12 (1H, m); 7.19-7.45 (12H, m); 7.58 (1H, d, J=8.1 Hz); 8.05 (1H, s); MS m/e (ES^+): 424.4 (30%), 423.4 (100%, $M^+ + H$); (ES^-): 422.3 (30%, M^-), 421.3 (100%, $M^- - H$); Analysis calculated for $C_{27}H_{26}N_4O$: C, 76.75; H, 6.20; N, 13.26%. Found: C, 76.58; H, 6.14; N, 13.24%.

EXAMPLE 15.

3-(1H-Indol-3-yl)-2-(3-nitro-benzylamino)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

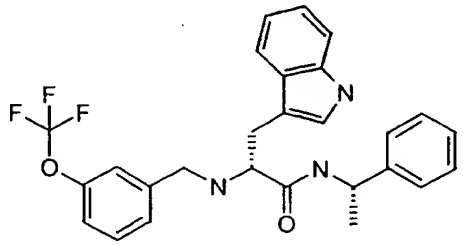


To a stirred solution of 3-nitrobenzaldehyde (332g, 2.2mmol) in 1,2-dichloroethane (60mL) was added intermediate V (614mg, 2mmol) followed by sodium triacetoxyborohydride (594mg, 2.8mmol). After stirring over night the reaction was cautiously quenched with saturated $NaHCO_3$ (20mL) and extracted with CH_2Cl_2 (3 x 50mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 45% EtOAc in heptane as eluent. The solvent was removed under reduced pressure to give pure product as a glass (648mg, 73%); IR (film): 3317, 2925, 1652, 1526, 1456, 1349, 733 cm^{-1};NMR ($CDCl_3$): δ 1.43 (3H, d, J=6.8 Hz); 1.85-1.95 (1H, br.s); 2.90 (1H, d.d, J=14.5 and 9.1 Hz); 3.33 (1H, d.d, J=14.4 and 4.4 Hz); 3.43 (1H, d.d, J=9.0 and 4.5 Hz); 3.65 (1H, d, J=14.2 Hz); 3.83 (1H, d, J=14.2 Hz); 5.09-5.17 (1H, m); 6.94 (1H, d, J=2.4 Hz); 7.06 (1H, t, J=7.5 Hz); 7.18 (1H, t, J=7.5 Hz); 7.22-7.40 (10H, m); 7.87 (1H, m); 7.97-8.10 (2H, m); MS m/e (ES^+): 444.4

(30%), 443.4 (100%, M^+ + H); Analysis calculated for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66%. Found: C, 70.55; H, 5.88; N, 12.67%.

EXAMPLE 16.

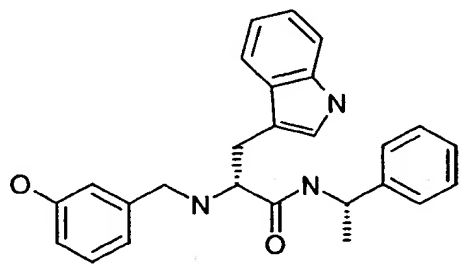
3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-(3-trifluoromethoxy-benzylamino)-propionamide, [R-(R*,S*)]



Method as for Example 13. Chromatography on normal phase silica using 35% EtOAc in heptane as the eluent and subsequent removal of the solvent under reduced pressure gave pure product as a glass (130mg, 54%); IR (film): 3307, 3060, 2974, 2925, 1652, 1589, 1516, 1495, 1456, 1260, 1217, 1164, 1012, 743 cm^{-1}; NMR ($CDCl_3$): δ 1.40 (3H, d, J=6.8 Hz); 1.60-2.00 (1H, br.s); 2.97 (1H, d.d, J=14.7 and 8.8 Hz); 3.29-3.35 (1H, m); 3.48 (1H, d.d, J=8.8 and 4.6 Hz); 3.62 (1H, d, J=13.9 Hz); 3.74 (1H, d, J=13.9 Hz); 5.07-5.15 (1H, m); 6.91 (1H, d, J=2.2 Hz); 6.96-7.39 (13H, m); 7.63 (1H, d, J=7.8 Hz); 7.97 (1H, m); MS m/e (ES^+): 483.4 (30%), 482.4 (100%, M^+ + H); Analysis calculated for $C_{27}H_{26}N_3O_2F_3$: C, 67.35; H, 5.44; N, 8.73%. Found: C, 67.31; H, 5.43; N, 8.67%.

EXAMPLE 17.

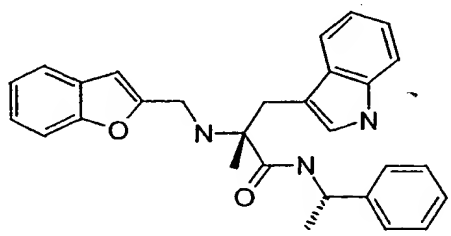
2-(3-Hydroxy-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



Method as for Example 13. Chromatography on normal phase silica using 40% EtOAc in heptane as the eluent and subsequent removal of the solvent under reduced pressure gave pure product as a glass (94mg, 45%); IR (film): 3317, 3059, 2975, 2926, 1645, 1589, 1520, 1456, 1266, 1159, 743 cm^{-1}; NMR ($CDCl_3$): δ 1.40 (3H, d, J=7.1 Hz); 1.70-1.90 (1H, br.s); 2.89 (1H, d.d, J=14.5 and 9.4 Hz); 3.33 (1H, d.d, J=14.7 and 4.2 Hz); 3.49-3.54 (1H, m); 3.53 (1H, d, J=13.9 Hz); 3.69 (1H, d, J=13.9 Hz); 5.00-5.20 (2H, m); 6.28 (1H, d, J=1.7 Hz); 6.60 (1H, d, J=7.6 Hz); 6.65 (1H, d.d, J=7.9 and 2.0 Hz); 6.89 (1H, d, J=2.2 Hz); 7.06 (1H, t, J=7.8 Hz); 7.09-7.13 (1H, m); 7.19-7.52 (7H, m); 7.54 (1H, d, J=8.5 Hz); 7.64 (1H, d, J=8.5 Hz); 8.05 (1H, m); MS m/e (ES^+): 415.4 (30%), 414.4 (100%, M^+ + H); Analysis calculated for $C_{26}H_{27}N_3O_2$: C,75.52; H, 6.58; N, 10.16%. Found: C, 75.28; H, 6.61; N, 10.03%.

EXAMPLE 18.

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

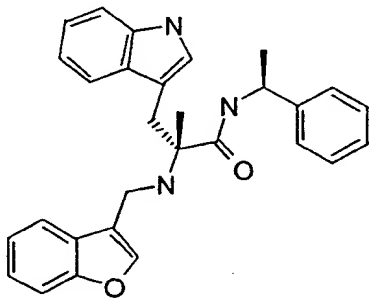


To a stirred solution of 2-benzofurancarboxaldehyde (3.19g, 21.8mmol) in 1,2-dichloroethane (150mL) was added 2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide (prepared as described by Boyle S. *et al.*, Bioorg. Med. Chem. 2:357, 1994) (5g, 15.6mmol), followed by sodium triacetoxyborohydride (6.6mg, 31.2mmol). After stirring over night the reaction was cautiously quenched with 2N NaOH (150mL) and extracted with CH_2Cl_2 (3 x 200mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 30% EtOAc in heptane as eluent and then on reverse phase silica using 70% MeOH in H_2O as eluent. Crystallization from ether gave pure product (5.55g, 79%); mp 118-121°C: $[\alpha)_D^{20}$=+12.5° (*c*=1, MeOH); IR (film): 3329, 3059, 2975, 2926, 1652, 1506, 1455, 1371,

1354, 1342, 1255, 1170, 1105, 1010, 938, 743 cm^{-1}; NMR ($CDCl_3$): δ 1.47 (3H, s); 1.47 (3H, d, J=6.8 Hz); 1.89 (1H, s); 3.16 (2H, s); 3.78 (1H, br.d, J=12.9 Hz); 3.86 (1H, d, J=14.4 Hz); 5.05-5.13 (1H, m); 6.43 (1H, s); 6.87 (1H, d, J=2.2 Hz); 7.09-7.40 (11H, m); 7.47-7.50 (1H, m); 7.65 (1H, d, J=7.8 Hz); 7.92 (1H, d, J=7.8 Hz); 7.96 (1H, s); MS m/e (ES^+): 453.1 (30%), 452.1 (100%, M^+ + H), 393.2 (15%); Analysis calculated for $C_{29}H_{29}N_3O_2$: C, 77.14; H, 6.47; N, 9.30%. Found: C, 77.14; H, 6.42; N, 9.36%.

EXAMPLE 19.

2-[(Benzofuran-3-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



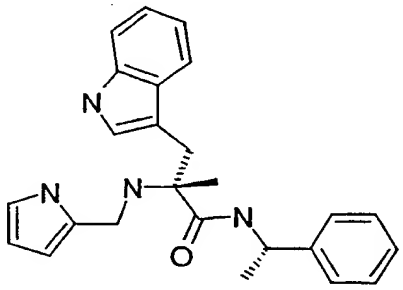
To a stirred solution of 3-benzofurancarboxaldehyde (146mg, 1mmol) (Ind. J. Chem., Vol. 31B, 1992, 526) in 1,2-dichloroethane (10mL) was added 2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide (321mg, 1mmol) followed by sodium triacetoxyborohydride (424mg, 2mmol). After stirring over night at room temperature another portion of sodium triacetoxyborohydride (424mg, 2mmol) was added. The reaction was heated to reflux for 4 h. Cooled to room temperature and cautiously quenched with saturated $NaHCO_3$ (100mL) and extracted with CH_2Cl_2 (3 x 20mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 25% EtOAc in heptane as eluent. Crystallization from ether/heptane gave pure product (232mg, 51%); mp 104-106°C: $[\alpha]_D^{23}$=-13.4° (*c*=1, MeOH); IR (film): 3418, 3314, 3058, 2976, 2927, 1652, 1505, 1452, 1371, 1354, 1341, 1279, 1266, 1186, 1095, 1010, 858, 743 cm^{-1}; NMR ($CDCl_3$): δ 1.40 (3H, d, J=6.8 Hz); 1.52 (3H, s); 1.71 (1H, s); 3.15 (1H, d, J=14.4 Hz); 3.27 (1H, d, J=14.4 Hz); 3.80 (1H, d, J=13.2 Hz); 3.88 (1H, d, J=13.2 Hz); 5.01-5.09 (1H, m); 6.79 (1H, d, J=2.2 Hz); 7.07-7.40 (12H, m); 7.44 (1H d.d, J=8.3 and 0.7 Hz); 7.65 (1H, d, J=7.8 Hz); 7.68 (1H, d, J=8.1 Hz); 7.93 (1H, s); MS m/e

(ES$^+$): 452.1 (100%, M$^+$ + H); Analysis calculated for $C_{29}H_{29}N_3O_2$: C, 77.14; H, 6.47; N, 9.30%.

Found: C, 76.91; H, 6.39; N, 9.26%.

EXAMPLE 20.

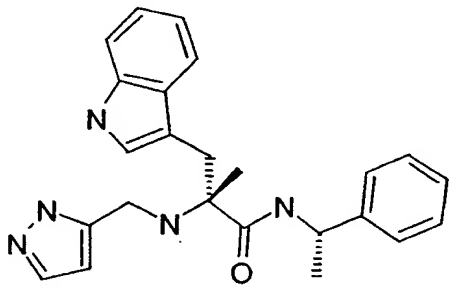
3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(1H-pyrrol-2-ylmethyl)-amino]-propionamide, [R-(R*,S*)]



To a stirred solution of 2-pyrrolecarboxaldehyde (71mg, 0.75mmol) in 1,2-dichloroethane (10mL) was added 2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide (161mg, 0.5mmol) followed by sodium triacetoxyborohydride (424mg, 2mmol). After stirring over night at room temperature the reaction was cautiously quenched with saturated $NaHCO_3$ (50mL) and extracted with CH_2Cl_2 (2 x 50mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using 40% EtOAc in heptane as eluent. Crystallization from ether/heptane gave pure product (50mg, 25%); mp 123-133°C; $[\alpha]_D^{23}$= (*c*=1, MeOH); IR (film): 3314, 2976, 2926, 2852, 1651, 1511, 1455, 909, 736 cm^{-1}; NMR ($CDCl_3$): δ 1.41 (3H, d, J=6.8 Hz); 1.45 (3H, s); 3.14 (1H, d, J=14.4 Hz); 3.29 (1H, d, J=14.4 Hz); 3.70 (1H, d, J=13.1 Hz); 3.76 (1H, d, J=12.9 Hz); 5.02-5.10 (1H, m); 5.97 (1H, s); 6.07-6.09 (1H, m); 6.58-6.60 (1H, m); 6.74 (1H, d, J=2.2 Hz); 7.10-7.35 (8H, m); 7.41 (1H d, J=7.6 Hz); 7.65 (1H, d, J=7.8 Hz); 7.89 (2H, s); MS m/e (ES$^+$): 423.2 (20%, M$^+$ + Na); 402.2 (30%); 401.2 (100%, M$^+$ + H); 322.2 (40%); Analysis calculated for $C_{25}H_{28}N_4O$: C, 74.97; H, 7.05; N, 13.99%. Found: C, 74.83; H, 7.05; N, 13.95%.

EXAMPLE 21.

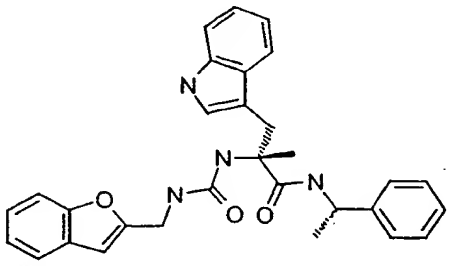
3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(2H-pyrazol-3-ylmethyl)-amino]-propionamide, [R-(R*,S*)]



To a stirred solution of pyrazole-3-carboxaldehyde (96mg, 1mmol, supplied as dimer) in pyridine (10mL) was added 2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide (161mg, 0.5mmol) followed by sodium triacetoxyborohydride (848mg, 4mmol). After stirring over night at room temperature another portion of sodium triacetoxyborohydride (424mg, 2mmol) was added. After stirring over night at room temperature the pyridine was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (100mL) and saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (100mL). The combined organic phases were washed with brine (50mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was initially purified by chromatography on normal phase silica using 95% EtOAc in heptane as eluent. The solvent was removed under reduced pressure and the residue was dissolved in aqueous acetonitrile and acidified using formic acid. Purification by chromatography on reverse phase silica using 25% CH_3CN in H_2O (0.1 % formic acid in mobile phases) as eluent gave pure product. The solvent was removed under reduced pressure and the residue was suspended between EtOAc and saturated $NaHCO_3$. The EtOAc was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give pure product as a glass (20mg, 10%); IR (film): 3260, 3059, 2979, 2927, 1651, 1515, 1456, 1374, 1266, 1105, 1048, 1011, 932, 741 cm^{-1}; NMR (DMSO-d_6): δ 1.22 (3H, s); 1.35 (3H, d, J=6.8 Hz); 2.26 (1H, s); 2.96-3.05 (2H, m); 3.50-3.75 (2H, m); 4.93 (1H, s); 6.10 (1H, s); 6.89-6.93 (2H, m); 7.00-7.04 (1H, m); 7.18-7.32 (6H, m); 7.35 (0.5H, s); 7.52 (1H, d, J=7.8 Hz); 7.60 (0.5H, s); 8.05-8.20 (1H, m); 10.82 (1H, s); 12.52 (0.5H, s); 12.73 (0.5H, s); MS m/e (ES^+): 424.1 (27%); 402.1 (100%, $M^+ + H$).

EXAMPLE 22.

2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]



Step 1

To a stirred solution of potassium hydroxide (6.6g, 100mmol, 85%) and hydroxylamine (3.66, 52.5mmol) in EtOH (100mL, 95%) and water (100mL) was added 2-benzofurancarboxaldehyde (7.34g, 50mmol). Stirred for 48 h before removing the EtOH under reduced pressure. The aqueous phase was saturated with NaCl and then extracted with EtOAc (2 x 300mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure. Crystallization from ether gave pure oxime (7.2g, 89%).

To an ice-cold solution of the oxime (3.22g, 20mmol) in THF (150mL, anhydrous) was added dropwise a solution of lithium aluminum hydride (20mL, 20mmol, 1M in THF) under an atmosphere of nitrogen. Reaction mixture allowed to reach room temperature and stirred over night. Reaction mixture cautiously quenched using water. Added 5N NaOH, and aqueous phase extracted with EtOAc (2 x 100mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by chromatography on normal phase silica using EtOAc as eluent to give intermediate IX (1.75g, 59%).

Step 2

A solution of the amine prepared in step 1 (1.358g, 9.23mmol) and pyridine (1.46, 18.5mmol) in CH_2Cl_2 (20mL, anhydrous) was added dropwise over 20 min to an ice cooled solution of triphosgene (0.96, 3.23mmol). Reaction mixture allowed to reach room temperature. After 30

min, solvent removed under reduced pressure. The residue was taken up in EtOAc, filtered, and solvent removed under reduced pressure to give isocyanate (1.60g, 100%). IR (film): 2256 cm^{-1}. A solution of the isocyanate (1.038g, 6mmol) and 2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide (1.926g, 6mmol) in THF (50mL, anhydrous) was stirred at room temperature for 5 min. The solvent was removed under reduced pressure. The residue was taken up in EtOAc and washed with 1N HCl (3x 20mL), saturated Na_2CO_3 (30mL), brine (30mL), dried $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by chromatography on reverse phase silica using 65% MeOH in H_2O as eluent. Crystallization from MeOH/H_2O gave pure product (1.35g, 45%). mp 176-178°C; $[\alpha]_D^{22}$=+30.4° (*c*=1, MeOH); IR (film): 3321, 3058, 2978, 2932, 1645, 1558, 1506, 1495, 1445, 1253, 741 cm^{-1}; NMR ($CDCl_3$): δ 1.35 (3H, d, J=6.8 Hz); 1.61 (3H, s); 3.20 (1H, d, J=14.6 Hz); 3.54 (1H, d, J=14.6 Hz); 4.38 (1H, d.d, J=16.0 and 6.0 Hz); 4.45 (1H, d.d, J=15.9 and 6.1 Hz); 4.78 (1H, t, J=6.0 Hz); 4.97 (1H, s); 4.95-5.05 (1H, m); 6.49 (1H, s); 6.76 (1H, d, J=2.4 Hz); 7.00 (1H, d, J=7.6 Hz); 7.05-7.10 (1H, m); 7.13-7.28 (9H, m); 7.38 (1H, d, J=8.1 Hz); 7.48-7.50 (1H, m); 7.57 (1H, d, J=7.8 Hz); 7.74 (1H, s); MS m/e (APCI$^+$): 496.3 (30%); 495.2 (100%, M^+ + H); 477.2 (7%); 374.2 (7%); 322.3 (17%); Analysis calculated for $C_{30}H_{30}N_4O_3$: C, 72.85; H, 6.11; N, 11.32%. Found: C, 73.09; H, 6.08; N, 11.35%.

EXAMPLES 23 TO 191 *(see Table 2 below)*

Intermediate VII, N-[b]benzofuranylmethyl-*R*-α-methyl-tryptophan-N-carboxyanhydride

Intermediate I (5.23g, 15mmol) was stirred in toluene (50mL) under nitrogen and heated to 55°C. Phosgene in toluene (37mL, 75mmol) was added in one portion and as soon as the temperature had returned to 55°C dry THF (150mL) was added rapidly dropwise. Stirring was continued for 30 min and the reaction was then cooled, the solvent removed *in vacuo*. The residue taken up in ether (50mL) and filtered and evaporated to dryness several times until a solid was obtained; (6.15g, 100%); IR (film): 3418, 1844, 1771, 1455, 1397, 1251, 986, 746cm^{-1}; NMR ($CDCl_3$) 1.64 (3H, s); 3.31 (1H, d, J=15 Hz); 3.44 (1H, d, J=15 Hz); 4.45 (1H, d J=16Hz); 4.81 (1H, d, J=16 Hz); 6.77 (1H, s); 6.94 (1H, d J=2.8 Hz); 7.14-7.58 (8H, m); 8.16 (1H, s).

General procedure for array synthesis of Examples 23 to 191

A 40-well DTI synthesizer rack (US 5324483) was loaded with 40 DTI vials (12 mL). To each vial 0.15 - 0.21 mmol of an amine or amine HCl salt was added. The rack was placed in a Cyberlab Liquid Handling Robot and to each vial 0.10 mmol N-[b]benzofuranylmethyl-*R*-α-methyl-tryptophan-N-carboxyanhydride (0.227 M in THF) was added. To those vials that contained amine HCl salts, 0.15 mmol triethylamine (0.254 M in THF) was added, in order to liberate the free amines. THF was then added to each vial to make up the total volume to 3 mL. The vials were placed in a 40-well DTI synthesizer equipped with a heating block, 40 condensers and a nitrogen manifold. The synthesizer was kept under a continuous flow of nitrogen and was shaken at 65°C on an orbital shaker for 2 days. The reactions were monitored by TLC (10% CH_3CN in CH_2Cl_2). The vials in which the reaction had gone to completion were taken out. To the remaining vials CH_3CN (2mL) was added each and these were shaken at 85°C for 19 h. The vials in which the reaction had gone to completion were taken out. To the remaining vials pyridine (1mL) was added each and these were shaken at 105°C for 6 h followed by 15 h at 65°C. The vials were then concentrated at reduced pressure in a Speedvac and were purified by chromatography over a 12 mL LC-Si SPE cartridge containing 2 g silica (elution with 10% CH_3CN in CH_2Cl_2 followed by 20% CH_3CN in CH_2Cl_2, 5% methanol in CH_2Cl_2, 10% methanol in CH_2Cl_2, 20% methanol in CH_2Cl_2 and 50% methanol in CH_2Cl_2, depending on the polarity of the products). The products were subjected to LC-MS. Those products which did contain the desired molecular ion, but were not sufficiently pure (typically < 85%) were further purified by prep HPLC on a C18 reversed phase preparative column. The HPLC-purified products were re-analyzed by LC-MS to determine the purity. The 40 final products were analyzed by ^1H NMR.

EXAMPLES 192 TO 308 *(see Table 3 below)*

Intermediate II

Step 1

The compound was prepared as described for Intermediate I, step 1; (20.5g, 59%); NMR ($CDCl_3$) 2.10 (1H, s); 3.18 (2H, m); 3.60 (3H, s); 3.80-4.00 (2H, m); 6.43 (1H, s); 7.03-7.60 (9H, m); 8.00 (1H, s).

Step 2

The compound was prepared as described for Intermediate I; (7.02g, 85%); NMR (DMSO-D_6) 3.01-3.12 (2H, m); 3.52 (1H, m); 3.80 (1H, d, J=15 Hz); 3.80 (1H, d, J=14.8 Hz); 6.61 (1H, s); 6.93-7.54 (9H, m); 10.82 (1H, s).

General procedure for array synthesis of Examples 192 to 308 *(see Table 4 below)*

A 40-well DTI synthesizer rack was loaded with 40 Kimble vials (10 mL). To each vial approximately 0.34 g (0.10 mmol) N-[b]benzofuranylmethyl-*R*-tryptophan was added followed by 1.5 equivalent of an amine or amine HCl salt. The rack was placed in a Cyberlab Liquid Handling Robot and to each vial 1.0 equivalent of HBTU (0.4 M in DMF) was added followed by 1.5 equivalent of diisopropylethylamine (0.5 M in DMF). To those vials, which contained amine HCl salts, an additional equivalent of diisopropylethylamine was added. DMF was added to make the total volume up to 1.5 mL. The vials were capped and the rack was shaken on an orbital shaker at room temperature for 3 h. To each vial, water (1mL) was added and the mixtures were purified on 3 mL LC-18 reversed phase SPE cartridges containing 500 mg of sorbent, using an ASPEC XL4 robot. The cartridges were conditioned with methanol (4mL) followed by methanol/water 1:1 (4mL). Water (1mL) was loaded onto the cartridges and the crude reaction mixtures were loaded into the water layer. The cartridges were washed with water (4mL) and methanol/water 1:1 (4mL) and were eluted with methanol (4mL). The methanol fractions were concentrated and the products were subjected to LC-MS. Those products which did contain the desired molecular ion, but were not sufficiently pure (typically <90%) were further purified by prep HPLC on a C18 reversed phase preparative column. The HPLC-purified products were re-analyzed by LC-MS to determine the purity. The 40 final products were analyzed by ^{1}H NMR.

EXAMPLES 309 TO 405 *(see Table 5 below)*

General procedure for array synthesis of Examples 309 to 405

The N-terminal derivatives where prepared from 2-amino-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, prepared as described by Boyle S., *et al.*, Bioorg. Med. Chem. **2**:357 (1994), or from 2-amino-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (Intermediate V), using the procedure of Siegel M.G., *et al.*, Tet. Lett. **38**: 3357, (1997).

Because the compounds are potent ligands to the NK_1 receptor, they are effective at displacing substance P at that position, and therefore are useful for treating biological conditions otherwise mediated by substance P. Accordingly, compounds capable of antagonising the effects of substance P at NK_1 receptors will be useful in treating or preventing a variety of brain disorders including pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, and addiction disorders; inflammatory diseases such as arthritis, asthma, and psoriasis; gastrointestinal disorders including colitis, Crohn's disease, irritable bowel syndrome and satiety; allergic responses such as eczema and rhinitis; vascular disorders such as angina and migraine; neuropathological disorders including scleroderma and emesis. The compounds of the invention, NK_1 receptor antagonists, are also useful as anti-angiogenic agents, for the treatment of conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth. They will also be useful as agents for imaging NK_1 receptors in vivo in conditions such as ulcerative colitis and Crohn's disease.

The compounds of the present invention are highly selective and competitive antagonists of the NK_1 receptor. They have been evaluated in an NK_1-receptor binding assay which is described below.

Human lymphoma IM9 cells were grown in RPMI 1640 culture medium supplemented with 10% fetal calf serum and 2mM glutamine and maintained under an atmosphere of 5% CO_2. Cells were passaged every 3-4 days by reseeding to a concentration of 4-8 x 10^6 / 40 ml per 175 cm^2 flask. Cells were harvested for experiments by centrifugation at 1000 g for 3 min. Pelleted cells were washed once by resuspension into assay buffer (50mM Tris HCl pH 7.4, 3mM $MnCl_2$, 0.02% BSA, 40mg/mL bacitracin, 2mg/mL chymostatin, 2mM phosphoramidon, 4mg/mL leupeptin) and repeating the centrifugation step before resuspending at a concentration of 2.5 x 10^6 cells/mL assay buffer. Cells (200ml) were incubated with [^{125}I]Bolton-Hunter substance P (0.05-0.1 nM) in the presence and absence of varying concentrations of test compounds for 50 min at 21°C. Non-specific binding (10% of the total binding observed under these conditions) was defined by 1mM [Sar^9, $Met(O_2)^{11}$] substance P. Reactions were terminated by rapid filtration under vacuum onto GF\C filters presoaked in 0.2% PEI for 1-2 h, using a Brandel cell harvester. Filters were washed with 6 x 1ml ice-cold Tris HCl (50mM, pH 7.4) and radioactivity bound determined

using a gamma counter. Results were analyzed using iterative curve fitting procedures in RS1 or Graphpad Inplot.

Table 1: In Vitro Human NK_1 Receptor Binding Assay

Example No	**NK_1 binding IC_{50} (nM)**
1	591
2	23
3	6
4	1213
5	295
6	0.7
7	3.3
8	27
9	112
10	51
11	46
12	14
13	35
14	4.7
15	>10,000
16	9.1
17	344
18	4.4
19	58
20	815
21	1808
22	2.9

Similar binding data are presented in Tables 2-5 for specific invention compounds.

Table 2: Examples 23-191

Ex.	Name	Yield (mg)	Mol. ion	lcms % purity	lcms Rt (min)	IC_{50} (nM) hNK_1
23	2-[(Benzofuran-2-ylmethyl)-amino]-3 (1H-indol-3-yl)-2-methyl-N-pyridin-2 ylmethyl-propionamide	19,7	439	100	3,07	1284
24	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-pyridin-3-ylmethyl-propionamide	23,5	439	100	2,6	547
25	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-pyridin-4-ylmethyl-propionamide	41,9	439	100	2,6	131
26	2-[(Benzofuran-2-ylmethyl)-amino]-N-cyclohexyl-3-(1H-indol-3-yl)-2-methyl-propionamide	18,4	430	100	5,2	1011
27	2-[(Benzofuran-2-ylmethyl)-amino]-N-cyclohexylmethyl-3-(1H-indol-3-yl)-2-methyl-propionamide	24,6	444	100	5,81	311
28	2-[(Benzofuran-2-ylmethyl)-amino]-N-benzyl-3-(1H-indol-3-yl)-2-methyl-propionamide	26,5	438	97	4,6	44
29	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-1-phenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	43,1	468	82	3,22	7
30	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4-chloro-phenyl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	43,3	486	74	5,81	17
31	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-naphthalen-1-yl-ethyl)-propionamide	29,4	502	100	6,05	>10,000
32	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-naphthalen-1-yl-ethyl)-propionamide	40,1	502	100	5,96	>10,000

33	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4-fluoro-phenyl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	44,4	470	100	5,11	9
34	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-(4-nitro-phenyl)-ethyl]-propionamide	23,8	497	100	5,07	14
35	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[1-(4-methoxy-phenyl)-ethyl]-2-methyl-propionamide	27,8	482	100	4,86	31
36	N-[1-(2-Amino-phenyl)-ethyl]-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	25,8	467	100	4,45	1620
37	N-[1-(3-Amino-phenyl)-ethyl]-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	25,5	467	100	3,7	364
38	N-[1-(4-Amino-phenyl)-ethyl]-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	22,5	467	100	3,2	141
39	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4-dimethylamino-phenyl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	48,3	495	100	5,26	863
40	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(3-dimethylamino-phenyl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	25,3	495	100	5,18	1065
41	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-thiophen-3-yl-ethyl)-propionamide	17	458	100	4,89	19
42	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	34,5	452	100	5,06	261

43	2-{[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionylamino]-methyl}-4-hydroxy-pyrimidine-5-carboxylic acid	28,5	500	10	9,4	3613
44	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-3-yl-ethyl)-propionamide	43,9	453	90	6,85	151
45	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-pyridin-2-yl-ethyl)-propionamide	43	453	95	7,15	913
46	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,4-dichloro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	49,5	506	95	10,2	1560
47	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(4-sulfamoyl-phenyl)-ethyl]-propionamide	52,6	531	95	6,66	7616
48	N-(2-Amino-6-fluoro-benzyl)-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	49,3	471	95	8,68	6423
49	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-cyclohexylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	4,9	460	95	8,22	1550
50	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-2-phenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	44,4	468	95	7,6	1333
51	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3,5-bis-trifluoromethyl-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	31,1	574	95	10,32	179

52	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-propionamide	39,3	459	95	9,16	>10,000
53	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-phenethyl-propionamide	42	452	90	8,9	262
54	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,3-dimethyl-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	23,2	466	90	9,95	834
55	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(3-methoxy-benzyl)-2-methyl-propionamide	49	468	95	8,95	643
56	N-[2-(4-Amino-phenyl)-ethyl]-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	49	467	90	7,31	3228
57	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	7	458	95	10,73	290
58	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-p-tolyl-ethyl)-propionamide	27	466	90	9,95	624
59	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(3-trifluoromethoxy-benzyl)-propionamide	46	522	90	9,61	>10,000
60	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-dimethylamino-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	10	481	90	9,16	964
61	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-fluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	48,4	456	90	8,74	61
62	N-(4-Amino-benzyl)-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-	32,3	453	90	7,29	837

	propionamide					
63	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-propyl)-propionamide	21,6	466	75	9,95	58
64	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-chloro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	50,2	472	90	9,3	76
65	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-bromo-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	43,9	516	90	9,43	700
66	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(4-trifluoromethoxy-benzyl)-propionamide	40,9	522	90	9,69	3444
67	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-p-tolyl-ethyl)-propionamide	18,8	466	92	9,94	3
68	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(4-methoxy-benzyl)-2-methyl-propionamide	48,9	468	90	8,41	312
69	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-ethyl)-propionamide	44,7	453	95	7,68	112
70	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	38,1	458	90	10,45	216
71	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(4-methyl-benzyl)-propionamide	40	452	90	9,13	144
72	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-bromo-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	43,2	516	90	9,43	18

73	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-2-phenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	35,2	468	90	7,56	1229
74	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(3-trifluoromethyl-benzyl)-propionamide	16	506	90	9,51	12
75	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1,2-diphenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	48,1	528	100	7,06	>10,000
76	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-methylamino-ethyl)-propionamide	28	405	50	2,01	3696
77	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-chloro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	20	472	100	6,19	17
78	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1,3,5-triaza-tricyclo[3.3.1.1>3,7]-dec-7-yl)-propionamide	9,2	485	50	1,93	>10,000
79	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-methyl-2-(3-trifluoromethyl-phenyl)-ethyl]-propionamide	30,1	534	100	6,84	>10,000
80	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-2-pyridin-2-yl-ethyl)-propionamide	22,4	529	100	5,9	>10,000
81	4-{[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionylamino]-methyl}-3-methoxy-benzoic acid methyl ester	37,4	526	100	5,59	>10,000
82	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1,2,2-trimethyl-propyl)-	8,5	432	100	6,51	1144

	propionamide					
83	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-dimethylamino-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	27,5	419	100	3,61	3519
84	4-[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionylamino]-3-(4-chloro-phenyl)-butyric acid	5	544	100	1,62	>10,000
85	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(3-oxo-2,3-dihydro-1H-isoindol-1-yl)-propionamide	11,3	479	100	3,73	2443
86	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(2-oxo-imidazolidin-1-yl)-ethyl]-propionamide	24,7	460	100	2,58	>10,000
87	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[3-(4-pyridin-2-yl-piperazin-1-yl)-propyl]-propionamide	38,9	551	100	4,63	>10,000
88	2-[(Benzofuran-2-ylmethyl)-amino]-N-[4-(2,6-dimethyl-piperidin-1-yl)-butyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	33,4	515	100	4,58	>10,000
89	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-piperidin-1-ylmethyl-cyclohexyl)-propionamide	21,2	527	100	8,88	6735
90	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(1H-imidazol-4-yl)-1-methyl-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	8,2	456	100	3,07	>10,000

91	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-propionamide	28,1	473	100	3,07	>10,000
92	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-isopropyl-2-methyl-propionamide	17,6	390	100	4,96	2285
93	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-methyl-2-(2-oxo-pyrrolidin-1-yl)-ethyl]-propionamide	17,6	473	100	3,29	>10,000
94	2-[(Benzofuran-2-ylmethyl)-amino]-N-[4-(2,5-dimethyl-pyrrolidin-1-yl)-butyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	30,6	501	100	3,27	>10,000
95	N-[2-(5-Amino-1H-imidazol-4-yl)-2-oxo-ethyl]-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	19,2	471	100	3,5	>10,000
96	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(2-oxo-oxazolidin-3-yl)-ethyl]-propionamide	4,6	461	100	2,26	>10,000
97	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(1H-imidazol-4-yl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	30	442	100	2,26	>10,000
98	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,2-diphenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	34,5	528	100	2,26	>10,000
99	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-propionamide	17,9	459	100	2,26	>10,000

100	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(5-nitro-furan-2-ylmethyl)-propionamide	7,2	473	100	2,26	390
101	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(5-methyl-1H-imidazol-4-yl)-ethyl]-propionamide	19,4	456	100	2,27	>10,000
102	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(3-dimethylamino-phenyl)-cyclopentylmethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	18,9	549	90	8,66	>10,000
103	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1H-benzoimidazol-2-ylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	0,4	478	77	0 05	74
104	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	8,3	458	100	0 06	8
105	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-[1,3]dioxolan-2-ylmethyl)-propionamide	13,2	510	69	0 05	>10,000
106	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-3-ylmethyl)-propionamide	5,7	507	100	0 06	4630
107	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-cyclopropyl)-propionamide	14	464	100	0 05	4145
108	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1,2,3,4-tetrahydro-isoquinolin-3-ylmethyl)-propionamide	0,6	493	100	0 05	4566

109	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,5-dichloro-thiophen-3-ylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	30,3	512	100	0 06	279
110	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-cyclopropylmethyl)-propionamide	19,7	478	100	0 05	1141
111	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-propionamide	1	478	100	0 08	>10,000
112	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(3-nitro-benzyl)-propionamide	3	483	100	0 06	12
113	2-[(Benzofuran-2-ylmethyl)-amino]-N-indan-2-yl-3-(1H-indol-3-yl)-2-methyl-propionamide	10,1	464	100	0 05	463
114	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-thiophen-2-yl-propyl)-propionamide	2,5	472	90	0 05	128
115	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-furan-2-yl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	11,5	442	95	0 05	154
116	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-hydroxy-cyclohexylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	5,6	460	100	0 05	>10,000
117	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-furan-2-yl-cyclobutylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	14,2	482	100	0 06	>10,000
118	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(5-chloro-thiophen-2-yl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	15	492	100	0 06	45

119	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(4-nitro-benzyl)-propionamide	4,1	483	100	0 07	89
120	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(1H-indazol-3-yl)-1-methyl-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	0,7	506	94	0 06	2652
121	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-pyrrol-1-yl-ethyl)-propionamide	15	441	100	0 05	654
122	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(2,5-dichloro-thiophen-3-yl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	8,7	526	100	0 08	442
123	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(octahydro-indol-1-yl)-ethyl]-propionamide	7,3	499	63	0 04	>10,000
124	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-(4-nitro-phenyl)-ethyl]-propionamide	2,6	497	100	0 07	92
125	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-piperidin-1-yl-ethyl)-propionamide	29,5	459	97	0 04	>10,000
126	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-methyl-[1,3]dioxolan-2-ylmethyl)-propionamide	28	448	95	0 07	6794
127	2-[(Benzofuran-2-ylmethyl)-amino]-N-furan-2-ylmethyl-3-(1H-indol-3-yl)-2-methyl-propionamide	23,9	427	100	0 05	191
128	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-morpholin-4-yl-ethyl)-propionamide	31,7	461	95	0 03	>10,000

129	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(3-methyl-benzyl)-propionamide	37,7	452	100	0 06	43
130	2-[(Benzofuran-2-ylmethyl)-amino]-N-indan-1-yl-3-(1H-indol-3-yl)-2-methyl-propionamide	37,8	464	100	0 05	163
131	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-methyl-2-piperidin-1-yl-propyl)-propionamide	31,6	487	100	0 08	>10,000
132	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[2-(2-thioxo-imidazolidin-1-yl)-ethyl]-propionamide	24,6	476	97	0 02	6035
133	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-methyl-2-phenyl-propyl)-propionamide	5	480	87	0 06	4479
134	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-imidazol-1-yl-propyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	27,3	456	100	0 02	5368
135	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(tetrahydro-furan-2-ylmethyl)-propionamide	13,5	432	100	0 03	1205
136	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-methyl-tetrahydro-furan-2-ylmethyl)-propionamide	26,6	446	95	0 02	>10,000
137	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-thiophen-2-ylmethyl-propionamide	33,6	444	96	0 03	100
138	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(tetrahydro-furan-2-ylmethyl)-propionamide	25,4	432	96	0 02	4867

139	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,5-difluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	41,7	474	93	0 05	99
140	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-propyl)-propionamide	31,8	466	100	0 05	>10,000
141	N-(4-Amino-naphthalen-1-ylmethyl)-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	11,6	503	95	0 03	2337
142	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,3-dimethoxy-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	19,3	498	96	0 03	1961
143	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(4-hydroxy-phenyl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	32,9	468	96	0 02	>10,000
144	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-hydroxymethyl-cyclopentyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	16,4	446	94	0 02	>10,000
145	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-pyridin-3-yl-ethyl)-propionamide	35,9	453	97	0 01	1301
146	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4,5-dihydro-furan-2-yl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	0,8	444	90	0 02	3587
147	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-piperazin-1-yl-ethyl)-propionamide	18,5	460	98	0 02	>10,000
148	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1,2,3,4-tetrahydro-naphthalen-1-yl)-propionamide	34,7	478	93	0 03	>10,000

149	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,5-dimethoxy-2,5-dihydro-furan-2-ylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	31,8	490	75	0 02	>10,000
150	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-propyl)-propionamide	32,4	466	95	0 04	2621
151	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-quinolin-3-ylmethyl-propionamide	2,4	489	100	0 02	1213
152	4-[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionylamino]-3-phenyl-butyric acid	9	510	94	0 01	>10,000
153	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	6,9	514	100	0 01	3555
154	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-pyrrolidin-3-ylmethyl-propionamide	6,1	431	5	0 04	>10,000
155	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-pyrrolidin-1-yl-ethyl)-propionamide	25,2	445	93	0 02	>10,000
156	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-piperidin-4-ylmethyl-propionamide	1,4	445	3	0 05	>10,000
157	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-methyl-benzyl)-propionamide	38,2	452	95	0 02	455
158	2-[(Benzofuran-2-ylmethyl)-amino]-N-indan-1-yl-3-(1H-indol-3-yl)-2-methyl-propionamide	21,4	464	96	0 02	2567
159	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-3-yl-cyclobutylmethyl)-	7	492	92	0 01	3757

	propionamide					
160	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-thiophen-2-yl-cyclohexyl)-propionamide	6,1	511	100	0 03	>10,000
161	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	12,3	484	100	0 01	>10,000
162	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-propyl)-propionamide	8,7	466	95	0 02	42
163	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-oxo-2-phenyl-ethyl)-propionamide	16,9	466	80	0 07	166
164	2-[(Benzofuran-2-ylmethyl)-amino]-N-(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	5,5	542	10	0 06	>10,000
165	2-[(Benzofuran-2-ylmethyl)-amino]-N-bicyclo[2.2.1]hept-2-ylmethyl-3-(1H-indol-3-yl)-2-methyl-propionamide	38,1	456	100	0 08	>10,000
166	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-fluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	41,9	456	95	0 07	37
167	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3,4-difluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	23,2	474	100	0 07	29
168	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-chloro-4-fluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	42,8	490	95	0 08	230

169	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4,6-dimethyl-pyridin-3-ylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	11,2	467	100	0 06	6016
170	2-[(Benzofuran-2-ylmethyl)-amino]-N-(5-bromo-2-hydroxy-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	49,6	533	100	0 08	2384
171	4-{[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionylamino]-methyl}-benzoic acid	28,7	482	95	0 06	>10,000
172	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-thiophen-2-yl-ethyl)-propionamide	36,8	458	100	0 07	153
173	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(2-morpholin-4-yl-2-oxo-ethyl)-propionamide	36,3	475	90	0 06	>10,000
174	N-Benzo[1,3]dioxol-5-ylmethyl-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	45,7	482	100	0 07	94
175	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3,4-dichloro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	21,4	507	90	0 08	96
176	2-[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionylamino]-3-(1H-imidazol-4-yl)-propionic acid methyl ester	44,3	453	100	0 07	1763
177	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-chloro-2-fluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	24,6	490	100	0 08	444
178	N-(3-Amino-benzyl)-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-	36,2	453	100	0 06	1373

	propionamide					
179	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,4-diamino-pyrimidin-5-ylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	3,1	470	56	0 06	5917
180	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-fluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	42	456	95	0 07	266
181	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,4-difluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	23,4	474	100	0 07	269
182	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3,4-dihydroxy-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	4,1	470	90	0 06	>10,000
183	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-hydroxymethyl-2-(1H-imidazol-4-yl)-ethyl]-3-(1H-indol-3-yl)-2-methyl-propionamide	1,7	472	33	0 05	>10,000
184	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-cyclohexylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	36,4	460	100	0 07	>10,000
185	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(3-morpholin-4-yl-propyl)-propionamide	28,5	475	100	0 06	>10,000
186	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	8,5	454	81	0 07	84
187	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-fluoro-4-methoxy-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	42,2	486	100	0 07	131

188	N-(2-Amino-4-methoxy-benzyl)-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-propionamide	10	483	96	0 06	2282
189	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-chloro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	47	472	94	0 07	1129
190	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,6-difluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	41,6	474	97	0 07	3537
191	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-chloro-4-fluoro-benzyl)-3-(1H-indol-3-yl)-2-methyl-propionamide	24,4	490	99	0 07	55

Table 3: Examples192-308

Ex.	Name	Yield (mg)	Mol. ion	lcms % purity	lcms Rt (min)	IC_{50} (nM) hNK_1
192	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-pyridin-2-ylmethyl-propionamide	26	425	100	3,94	1981
193	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-piperazin-1-yl-ethyl)-propionamide	27	446	94	1,04	>10,000
194	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-1-yl)-propionamide	41	464	100	5.63, 5.80	703
195	2-[(Benzofuran-2-ylmethyl)-amino]-N-indan-1-yl-3-(1H-indol-3-yl)-propionamide	23	450	100	5,39	1750
196	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-thiophen-2-yl-propyl)-propionamide	36	458	100	5,67	92

197	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-naphthalen-1-yl-ethyl)-propionamide	44	488	99	6,77	933
198	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-propionamide	31	445	99	2,27	>10,000
199	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(4-methoxy-benzyl)-propionamide	39	454	100	5,11	130
200	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(3-trifluoromethoxy-benzyl)-propionamide	34	508	96	6,19	355
201	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-imidazol-1-yl-propyl)-3-(1H-indol-3-yl)-propionamide	21	442	100	1,22	>10,000
202	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-pyrrolidin-3-ylmethyl-propionamide	6	417	98	4,3	2184
203	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-piperidin-4-ylmethyl-propionamide	22	431	96	1,26	>10,000
204	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,5-difluoro-benzyl)-3-(1H-indol-3-yl)-propionamide	18	460	100	5,53	68
205	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-quinolin-3-ylmethyl-propionamide	10	475	97	4,27	2315
206	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(1H-imidazol-4-yl)-ethyl]-3-(1H-indol-3-yl)-propionamide	16	428	98	2,31	6681
207	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-naphthalen-1-yl-ethyl)-propionamide	43	489	98	6,76	591

208	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[1-(5-methyl-thiophen-2-yl)-ethyl]-propionamide	31	458	100	5,94	15
209	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(4-methyl-benzyl)-propionamide	35	438	100	5,74	82
210	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-p-tolyl-ethyl)-propionamide	36	452	100	5,98	337
211	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-hydroxymethyl-cyclopentyl)-3-(1H-indol-3-yl)-propionamide	21	432	100	5	>10,000
212	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-pyrrol-1-yl-ethyl)-propionamide	18	427	96	5,21	658
213	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-morpholin-4-yl-ethyl)-propionamide	28	447	100	1,39	1256
214	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-dimethylamino-benzyl)-3-(1H-indol-3-yl)-propionamide	39	467	99	4,3	4015
215	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,5-dichloro-thiophen-3-ylmethyl)-3-(1H-indol-3-yl)-propionamide	9	498	97	6,61	70
216	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(5-nitro-furan-2-ylmethyl)-propionamide	2	459	11	5,07	>10,000
217	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4-dimethylamino-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	44	481	99	4.46, 4.78	819
218	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3,5-bis-trifluoromethyl-benzyl)-3-(1H-indol-3-yl)-propionamide	20	560	85	7,14	294

219	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-bromo-benzyl)-3-(1H-indol-3-yl)-propionamide	17	502	96	6,96	31
220	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-p-tolyl-ethyl)-propionamide	38	452	100	6,16	2
221	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(4-nitro-benzyl)-propionamide	37	469	100	5,67	23
222	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-pyrrolidin-1-yl-ethyl)-propionamide	30	431	100	1,64	>10,000
223	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(tetrahydro-furan-2-ylmethyl)-propionamide	36	418	100	4,65	>10,000
224	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-phenyl-cyclopropyl)-propionamide	9	450	100	6,05	2902
225	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-1-methyl-ethyl)-3-(1H-indol-3-yl)-propionamide	32	458	97	7,07	1341
226	2-[(Benzofuran-2-ylmethyl)-amino]-N-cyclohexylmethyl-3-(1H-indol-3-yl)-propionamide	33	430	100	6,23	54
227	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(3-dimethylamino-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	41	481	96	5.05, 5.36	182
228	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(3-trifluoromethyl-benzyl)-propionamide	31	492	100	6,63	82
229	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-chloro-4-fluoro-benzyl)-3-(1H-indol-3-yl)-propionamide	39	476	98	6,4	33

230	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[1-(1-methyl-1H-pyrrol-3-yl)-ethyl]-propionamide	38	441	100	5,54	21
231	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-pyridin-3-ylmethyl-propionamide	35	425	100	0 04	790
232	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-thiophen-2-ylmethyl-propionamide	30	430	100	0 06	63
233	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-phenyl-propyl)-propionamide	37	452	100	0 07	1998
234	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	37	438	100	0 07	75
235	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4-fluoro-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	40	456	100	0 07	3
236	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-thiophen-3-yl-ethyl)-propionamide	41	444	100	0 07	7
237	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-oxo-2-phenyl-ethyl)-propionamide	38	435	0	01 0	5341
238	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-fluoro-benzyl)-3-(1H-indol-3-yl)-propionamide	34	442	100	0 07	89
239	2-[(Benzofuran-2-ylmethyl)-amino]-N-indan-2-yl-3-(1H-indol-3-yl)-propionamide	36	450	100	0 07	243
240	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-pyridin-4-ylmethyl-propionamide	33	425	100	0 04	196
241	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-propionamide	29	444	100	0 07	2

242	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-methyl-benzyl)-propionamide	39	438	100	0 07	170
243	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(5-chloro-thiophen-2-yl)-ethyl]-3-(1H-indol-3-yl)-propionamide	44	478	100	0 07	15
244	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-fluoro-benzyl)-3-(1H-indol-3-yl)-propionamide	38	442	100	0 07	12
245	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[1-(4-nitro-phenyl)-ethyl]-propionamide	32	483	100	0 07	3
246	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-phenethyl-propionamide	39	438	100	0 07	77
247	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-thiophen-2-yl-ethyl)-propionamide	33	444	100	0 07	56
248	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-fluoro-benzyl)-3-(1H-indol-3-yl)-propionamide	37	442	100	0 07	6
249	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-1-phenyl-ethyl)-3-(1H-indol-3-yl)-propionamide	43	454	100	0 06	607
250	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1H-benzoimidazol-2-ylmethyl)-3-(1H-indol-3-yl)-propionamide	36	464	100	0 05	3413
251	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-furan-2-yl-ethyl)-3-(1H-indol-3-yl)-propionamide	4	428	95	0 06	129
252	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(3-methyl-benzyl)-propionamide	37	438	100	0 07	33

253	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-propionamide	25	464	81	0 07	3327
254	2-[(Benzofuran-2-ylmethyl)-amino]-N-benzyl-3-(1H-indol-3-yl)-propionamide	37	424	100	0 06	22
255	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[1-(4-methoxy-phenyl)-ethyl]-propionamide	41	468	100	0 07	9
256	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-benzyl)-3-(1H-indol-3-yl)-propionamide	5	440	68	0 05	>10,000
257	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-methyl-2-phenyl-propyl)-propionamide	35	466	100	0 07	>10,000
258	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-chloro-benzyl)-3-(1H-indol-3-yl)-propionamide	38	458	100	0 07	46
259	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-propyl)-propionamide	39	452	100	0 07	21
260	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(3-nitro-benzyl)-propionamide	32	469	100	0 06	14
261	2-[(Benzofuran-2-ylmethyl)-amino]-N-furan-2-ylmethyl-3-(1H-indol-3-yl)-propionamide	31	414	100	0 06	406
262	2-[(Benzofuran-2-ylmethyl)-amino]-N-indan-1-yl-3-(1H-indol-3-yl)-propionamide	41	450	100	0 07	86
263	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-chloro-benzyl)-3-(1H-indol-3-yl)-propionamide	36	458	100	0 07	9

264	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4-chloro-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	44	472	100	0 07	7
265	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-methyl-1-phenyl-ethyl)-propionamide	41	452	96	0 07	328
266	2-[(Benzofuran-2-ylmethyl)-amino]-N-bicyclo[2.2.1]hept-2-ylmethyl-3-(1H-indol-3-yl)-propionamide	39	442	100	0 07	633
267	N-Benzo[1,3]dioxol-5-ylmethyl-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-propionamide	40	468	100	0 06	55
268	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3,4-difluoro-benzyl)-3-(1H-indol-3-yl)-propionamide	39	460	91	0 07	10
269	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-pyridin-4-yl-ethyl)-propionamide	9	439	92	0 04	9
270	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-cyclohexyl)-3-(1H-indol-3-yl)-propionamide	19	432	100	0 04	>10,000
271	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[2-(4-methoxy-phenyl)-ethyl]-propionamide	33	468	98	0 05	196
272	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-hydroxymethyl-2-phenyl-ethyl)-3-(1H-indol-3-yl)-propionamide	42	468	99	0 05	336
273	2-[(Benzofuran-2-ylmethyl)-amino]-N-(4-hydroxy-cyclohexyl)-3-(1H-indol-3-yl)-propionamide	15	432	99	0 04	>10,000
274	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(2-fluoro-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	21	456	97	0 05	264

275	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-benzylsulfanyl-1-hydroxymethyl-ethyl)-3-(1H-indol-3-yl)-propionamide	38	514	100	0 05	2157
276	2-[(Benzofuran-2-ylmethyl)-amino]-N-cyclohexyl-3-(1H-indol-3-yl)-propionamide	10	416	84	0 05	655
277	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-cyclohexyl-1-hydroxymethyl-ethyl)-3-(1H-indol-3-yl)-propionamide	17	474	96	0 05	2198
278	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(3-phenyl-propyl)-propionamide	33	452	88	0 05	2379
279	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3,4-dichloro-benzyl)-3-(1H-indol-3-yl)-propionamide	8	493	86	0 06	30
280	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[2-(1H-indol-3-yl)-ethyl]-propionamide	25	477	97	0 05	2540
281	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[2-(4-nitro-phenyl)-ethyl]-propionamide	28	483	93	0 05	51
282	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(4-chloro-phenyl)-1-methyl-ethyl]-3-(1H-indol-3-yl)-propionamide	30	487	98	0 06	833
283	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(4-trifluoromethyl-benzyl)-propionamide	9	492	91	0 06	420
284	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(4-fluoro-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	33	456	98	0 05	62

285	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[1-(4-nitro-phenyl)-ethyl]-propionamide	32	483	99	0 05	246
286	4-{[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-methyl}-cyclohexanecarboxylic acid	6	474	62	0 05	>10,000
287	2-[(Benzofuran-2-ylmethyl)-amino]-N-(cyano-phenyl-methyl)-3-(1H-indol-3-yl)-propionamide	36	449	99	0 06	35
288	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(4-chloro-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	32	472	99	0 06	136
289	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-hydroxymethyl-2-phenyl-ethyl)-3-(1H-indol-3-yl)-propionamide	35	468	99	0 05	209
290	2-[(Benzofuran-2-ylmethyl)-amino]-N-[1-(4-bromo-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	37	517	100	0 06	8
291	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[2-(3-methoxy-phenyl)-ethyl]-propionamide	29	468	96	0 05	1337
292	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-trifluoromethyl-benzyl)-propionamide	3	492	90	0 06	1126
293	2-[(Benzofuran-2-ylmethyl)-amino]-N-[2-(3-fluoro-phenyl)-ethyl]-3-(1H-indol-3-yl)-propionamide	33	456	96	0 05	55
294	2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-propionamide	15	444	86	0 06	58
295	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-methoxymethyl-2-phenyl-ethyl)-	34	482	99	0 06	3531

	propionamide					
296	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-benzylsulfanyl-ethyl)-3-(1H-indol-3-yl)-propionamide	16	484	98	0 06	1338
297	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-[2-(1H-indol-3-yl)-1-methyl-ethyl]-propionamide	36	491	100	0 05	3612
298	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-chloro-benzyl)-3-(1H-indol-3-yl)-propionamide	22	458	99	0 06	221
299	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-1-phenyl-ethyl)-3-(1H-indol-3-yl)-propionamide	28	454	93	0 05	4
300	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-p-tolyl-ethyl)-propionamide	10	452	98	0 06	256
301	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2,4-difluoro-benzyl)-3-(1H-indol-3-yl)-propionamide	12	460	98	0 06	53
302	2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-bromo-benzyl)-3-(1H-indol-3-yl)-propionamide	25	503	98	0 06	174
303	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-fluoro-5-trifluoromethyl-benzyl)-3-(1H-indol-3-yl)-propionamide	7	510	88	0 06	17
304	[2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-propionylamino]-phenyl-acetic acid methyl ester	36	482	100	0 06	43
305	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(2-phenoxy-ethyl)-propionamide	30	454	99	0 06	400

306	N-(4-Amino-benzyl)-2-[(benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-propionamide	32	439	99	0 04	639
307	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-methyl-3-phenyl-propyl)-propionamide	36	466	99	0 06	392
308	2-[(Benzofuran-2-ylmethyl)-amino]-N-(3-hydroxy-benzyl)-3-(1H-indol-3-yl)-propionamide	6	440	94	0 05	731

Table 4: Examples 309-359

Ex.	Name	Yield (mg)	Mol. ion	lcms % purity	lcms Rt (min)	IC_{50} (nM) hNK_1
309	3-(1H-Indol-3-yl)-2-methyl-2-[(naphthalen-2-ylmethyl)-amino]-N-(1-phenyl-ethyl)-propionamide	30,51	462	50	6,44	169
310	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(pyridin-2-ylmethyl)-amino]-propionamide	37,02	413	83	4,74	3325
311	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(quinolin-2-ylmethyl)-amino]-propionamide	31,53	463	84	5,96	88
312	2-[(Furan-3-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	28	402	78	4,9	1820
313	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(pyridin-4-ylmethyl)-amino]-propionamide	41,02	452	8	6,02	50
314	2-[(Furan-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	27,6	402	74	4,82	141

315	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(quinolin-3-ylmethyl)-amino]-propionamide	3,13	463	12	3,78	1068
316	2-[(1H-Benzoimidazol-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	58,59	452	16	4,63	>10,000
317	3-(1H-Indol-3-yl)-2-[(5-methoxy-benzofuran-2-ylmethyl)-amino]-2-methyl-N-(1-phenyl-ethyl)-propionamide	33,16	482	75	7,29	>10,000
318	3-(1H-Indol-3-yl)-2-[(isoquinolin-4-ylmethyl)-amino]-2-methyl-N-(1-phenyl-ethyl)-propionamide	8,84	463	55	3,28	1596
319	3-(1H-Indol-3-yl)-2-[(6-methoxy-benzofuran-2-ylmethyl)-amino]-2-methyl-N-(1-phenyl-ethyl)-propionamide	5,15	482	65	7,22	2098
320	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(pyridin-3-ylmethyl)-amino]-propionamide	20,2	413	72	2,51	5972
321	2-{2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-ethylamino}-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	20,67	552	96	0 05	3040
322	2-(3-Furan-2-yl-allylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	2,88	428	47	0 05	91
323	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[2-(pyridin-2-ylmethoxy)-benzylamino]-propionamide	28,74	519	69	0 05	3183
324	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[2-(pyridin-3-ylmethoxy)-benzylamino]-propionamide	32,96	519	88	0 04	2971

325	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(5-styryl-furan-2-ylmethyl)-amino]-propionamide	42,66	504	77	0 06	72
326	2-(4-Chloro-3-methylsulfamoyl-benzylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	8,05	539	83	0 05	4827
327	5-(4-{[2-(1H-Indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-phenoxy)-2,2-dimethyl-pentanoic acid	7,02	556	92	0 05	>10,000
328	3-(1H-Indol-3-yl)-2-methyl-2-{[4-(4-methyl-pent-2-enyl)-cyclohex-3-enylmethyl]-amino}-N-(1-phenyl-ethyl)-propionamide	17,49	498	86	0 07	>10,000
329	(2-{[2-(1H-Indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-phenyl)-carbamic acid ethyl ester	16,92	499	95	0 05	4188
330	2-(4-Chloro-2-methylsulfamoyl-benzylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	7,56	539	89	0 05	1100
331	2-[4-(2-Dimethylamino-ethoxy)-benzylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	24,9	499	65	0 03	>10,000
332	2-(2,3-Diphenyl-propylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	10,84	516	98	0 06	4944
333	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(1-phenyl-1H-indol-2-ylmethyl)-amino]-propionamide	16,98	516	98	0 06	3606

334	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[4-(4-phenyl-piperidin-1-yl)-benzylamino]-propionamide	19,88	527	74	0 06	>10,000
335	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-benzylamino]-propionamide	38,16	571	65	0 06	>10,000
336	2-(4-Chloro-3-sulfamoyl-benzylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	5,2	525	79	0 03	4229
337	4-{[2-(1H-Indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-benzoic acid methyl ester	20,24	525	81	0 04	1920
338	2-(2,3-Diphenyl-allylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	20,13	470	99	0 05	>10,000
339	2-(3-Benzo[1,3]dioxol-5-yl-allylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	24,74	514	54	0 06	343
340	2-[3-(4-Benzyloxy-phenyl)-allylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	24,64	482	72	0 05	4912
341	2-(4-Benzyloxy-benzylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	32,02	544	62	0 06	>10,000
342	Toluene-4-sulfonic acid 3-{[2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-phenyl ester	20,65	518	96	0 06	5091

343	2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	23,9	582	93	0 06	13
344	2-(3-Benzyloxy-benzylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	33,15	518	89	0 06	185
345	3-(1H-Indol-3-yl)-2-methyl-2-(4-methylsulfanyl-benzylamino)-N-(1-phenyl-ethyl)-propionamide	31,61	458	90	0 06	609
346	2-[(Anthracen-9-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	17,46	512	73	0 07	>10,000
347	3-(1H-Indol-3-yl)-2-methyl-2-(4-phenoxy-benzylamino)-N-(1-phenyl-ethyl)-propionamide	36,52	504	95	0 06	3382
348	2-[(Biphenyl-4-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	30,82	488	93	0 06	5562
349	2-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	33,19	456	94	0 06	356
350	2-[2-(4-Chloro-phenylsulfanyl)-benzylamino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	21,92	554	90	0 07	>10,000
351	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-(4-styryl-benzylamino)-propionamide	22,24	514	88	0 07	>10,000
352	2-(2,6-Dimethyl-octa-2,6-dienylamino)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	30,03	458	44	0 07	2212
353	3-(1H-Indol-3-yl)-2-methyl-2-{[5-(4-nitro-phenyl)-furan-2-ylmethyl]-amino}-N-(1-phenyl-ethyl)-propionamide	38,51	523	82	0 06	13

354	2-[(9H-Fluoren-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide	27,91	500	92	0 06	1731
355	3-(1H-Indol-3-yl)-2-[(1H-indol-3-ylmethyl)-amino]-2-methyl-N-(1-phenyl-ethyl)-propionamide	9,83	451	69	0 06	1047
356	3-(1H-Indol-3-yl)-2-methyl-2-(2-pentyl-3-phenyl-allylamino)-N-(1-phenyl-ethyl)-propionamide	33,02	508	86	0 07	>10,000
357	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(thiophen-2-ylmethyl)-amino]-propionamide	18,91	418	97	0 05	548
358	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(thiophen-3-ylmethyl)-amino]-propionamide	18,79	418	99	0 05	598
359	3-(1H-Indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-2-[(pyridin-4-ylmethyl)-amino]-propionamide	7,47	413	79	0 04	3712

Table 5: Examples 360-405

Ex.		**Yield (mg)**	**Mol. ion**	**lcms % purity**	**lcms Rt (min)**	**IC_{50} (nM) hNK_1**
360	2-(3-Furan-2-yl-allylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	12,16	414	59	0 06	>10,000
361	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[2-(pyridin-3-ylmethoxy)-benzylamino]-propionamide	14,01	505	79	0 04	729
362	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[(5-styryl-furan-2-ylmethyl)-amino]-propionamide	39,92	490	36	0 08	>10,000

363	2-(4-Chloro-3-methylsulfamoyl-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	18,8	526	86	0 06	490
364	5-(4-{[2-(1H-Indol-3-yl)-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-phenoxy)-2,2-dimethyl-pentanoic acid	12,49	543	79	0 07	1247
365	2-{[4-(4-Hydroxy-4-methyl-pentyl)-cyclohex-3-enylmethyl]-amino}-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	31,21	503	42	0 07	5278
366	3-(1H-Indol-3-yl)-2-{[4-(4-methyl-pent-2-enyl)-cyclohex-3-enylmethyl]-amino}-N-(1-phenyl-ethyl)-propionamide	38,13	484	65	0 09	4046
367	(2-{[2-(1H-Indol-3-yl)-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-phenyl)-carbamic acid ethyl ester	4,86	485	82	0 07	236
368	2-(2-Chloro-4-morpholin-4-yl-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	14,38	518	84	0 07	2239
369	2-(4-Chloro-2-methylsulfamoyl-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	53,07	526	83	0 06	450
370	2-(2,3-Diphenyl-propylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	11,18	502	73	0 08	534
371	3-(1H-Indol-3-yl)-2-[(4-oxo-4H-chromen-3-ylmethyl)-amino]-N-(1-phenyl-ethyl)-propionamide	16,18	466	66	0 07	>10,000
372	3-(1H-Indol-3-yl)-2-[(1-oxo-1,2,3,9-tetrahydro-4-thia-9-aza-fluoren-2-ylmethyl)-amino]-N-(1-phenyl-ethyl)-propionamide	9	523	26	0 08	>10,000

373	3-(1H-Indol-3-yl)-2-[(5-methyl-4-oxo-6-phenyl-4H-pyran-3-ylmethyl)-amino]-N-(1-phenyl-ethyl)-propionamide	17,38	506	2	0 07	507
374	4-{[2-(1H-Indol-3-yl)-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-benzoic acid methyl ester	33,82	456	95	0 06	1914
375	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[(2-propyl-5-pyrrol-1-yl-3H-imidazol-4-ylmethyl)-amino]-propionamide	28,55	495	76	0 05	165
376	2-(2,3-Diphenyl-allylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	14,27	500	76	0 08	>10,000
377	2-(3-Benzo[1,3]dioxol-5-yl-allylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	14,52	468	57	0 07	593
378	2-[3-(4-Benzyloxy-phenyl)-allylamino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	8,68	530	64	0 09	932
379	2-(4-Benzyloxy-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	15,05	504	80	0 08	587
380	3-(1H-Indol-3-yl)-2-(3-naphthalen-1-yl-propylamino)-N-(1-phenyl-ethyl)-propionamide	11,18	476	46	0 08	500
381	Toluene-4-sulfonic acid 3-{[2-(1H-indol-3-yl)-1-(1-phenyl-ethylcarbamoyl)-ethylamino]-methyl}-phenyl ester	24,84	568	92	0 08	>10,000
382	2-(3-Benzyloxy-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	44,62	504	91	0 08	>10,000
383	3-(1H-Indol-3-yl)-2-(4-methylsulfanyl-benzylamino)-N-(1-phenyl-ethyl)-propionamide	39,33	444	69	0 07	252

384	3-(1H-Indol-3-yl)-2-(4-phenoxy-benzylamino)-N-(1-phenyl-ethyl)-propionamide	32,52	490	83	0 08	2350
385	2-[(Biphenyl-4-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	24,28	474	90	0 08	1463
386	2-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	41,91	442	78	0 06	240
387	2-[2-(4-Chloro-phenylsulfanyl)-benzylamino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	48,88	541	96	0 09	201
338	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-(4-styryl-benzylamino)-propionamide	12,14	500	66	0 09	>10,000
389	2-(2,6-Dimethyl-octa-2,6-dienylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	50,41	444	5	0 08	2573
390	3-(1H-Indol-3-yl)-2-{[5-(4-nitro-phenyl)-furan-2-ylmethyl]-amino}-N-(1-phenyl-ethyl)-propionamide	7,86	509	44	0 07	50
391	2-[(9H-Fluoren-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	37,84	486	85	0 08	846
392	2-[(2,5-Dimethyl-1-phenyl-1H-pyrrol-3-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	5,27	491	3	0 08	>10,000
393	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[(pyridin-3-ylmethyl)-amino]-propionamide	03 2	399	71	0 04	802
394	3-(1H-Indol-3-yl)-2-[(naphthalen-2-ylmethyl)-amino]-N-(1-phenyl-ethyl)-propionamide	03 7	448	88	0 06	158

395	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[(pyridin-2-ylmethyl)-amino]-propionamide	02 9	399	74	0 05	>10,000
396	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[(thiophen-2-ylmethyl)-amino]-propionamide	04 3	404	98	0 05	1073
397	2-(3,4-Dimethoxy-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	03 3	458	65	0 05	>10,000
398	2-(3,5-Bis-trifluoromethyl-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	04 3	534	94	0 07	>10,000
399	2-(3,5-Difluoro-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	03 5	434	92	0 06	140
400	2-(3-Chloro-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	03 4	432	86	0 06	13
401	2-(3-Fluoro-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	03 4	416	87	0 06	39
402	2-[(Furan-3-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	03 0	388	84	0 05	881
403	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-(3-phenyl-propylamino)-propionamide	0 07	426	85	0 06	3907
404	3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-[(thiophen-3-ylmethyl)-amino]-propionamide	03 2	404	81	0 05	2390
405	2-[(Furan-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide	03 2	388	86	0 06	429

As noted above, the compounds of formula I will be best utilized in the form of pharmaceutical formulations. The following examples further illustrate specific formulations that are provided by the invention.

EXAMPLE 406

Tablet Formulation

Ingredient	Amount
3-[(benzofuran-2-ylmethyl)-amino]-3-(IH-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide,[R-(R*,S*)]	50 mg
potato starch	100 mg
talc	50 mg
magnesium carbonate	20 mg
dextrose	20 mg
	240 mg

The above ingredients are blended to uniformity and pressed into a tablet. Such tablets are administered to human subjects from one to four times a day for treatment of pain, depression and schizophrenia.

EXAMPLE 407

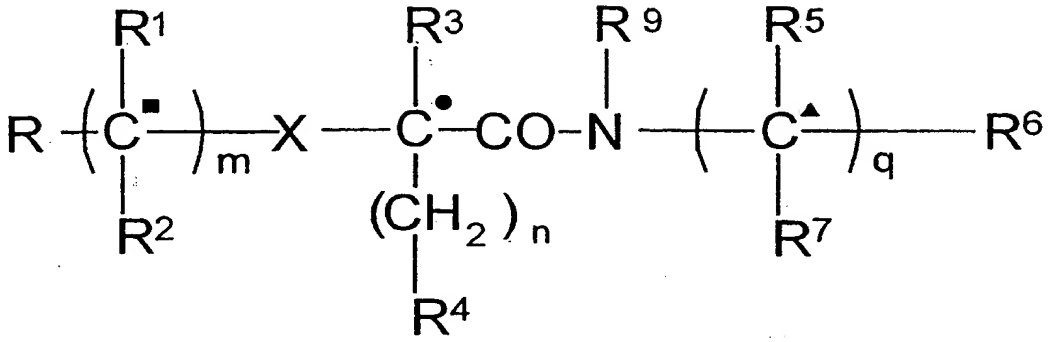
Capsules

Ingredient	Amount
The compound of Example 5	200 mg
Corn starch	100 mg
Sodium benzoate	10 mg
talc	50 mg
	360 mg

The ingredients are blended to uniformity and encapsulated into gelatin telescoping capsules. The capsules are administered to a human at the rate of one to three each day for treatment of rheumatoid arthritis, atheroclerosis, aberrant neovascularization, and for the inhibition of tumor cell growth.

We claim:

1. A compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein

■, ●, and ▲ indicate all stereoisomers,

R is:

pyridyl,

thienyl,

furyl,

pyrrolyl,

pyrazolyl,

quinolyl,

isoquinolyl,

naphthyl,

indolyl,

benzofuryl,

benzothiophenyl,

benzimidazolyl, and

benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by

alkyl,

hydroxy,

alkoxy,

halogen,

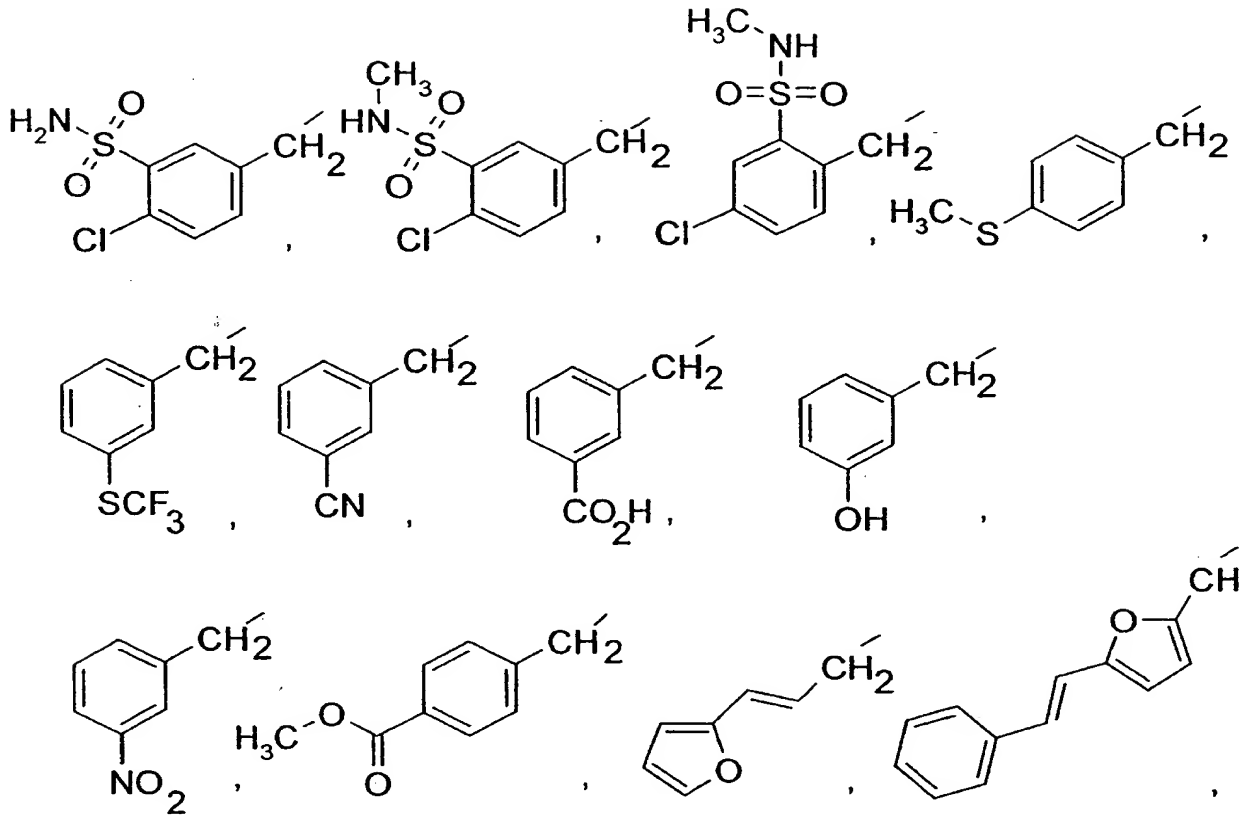
$-CF_3$,

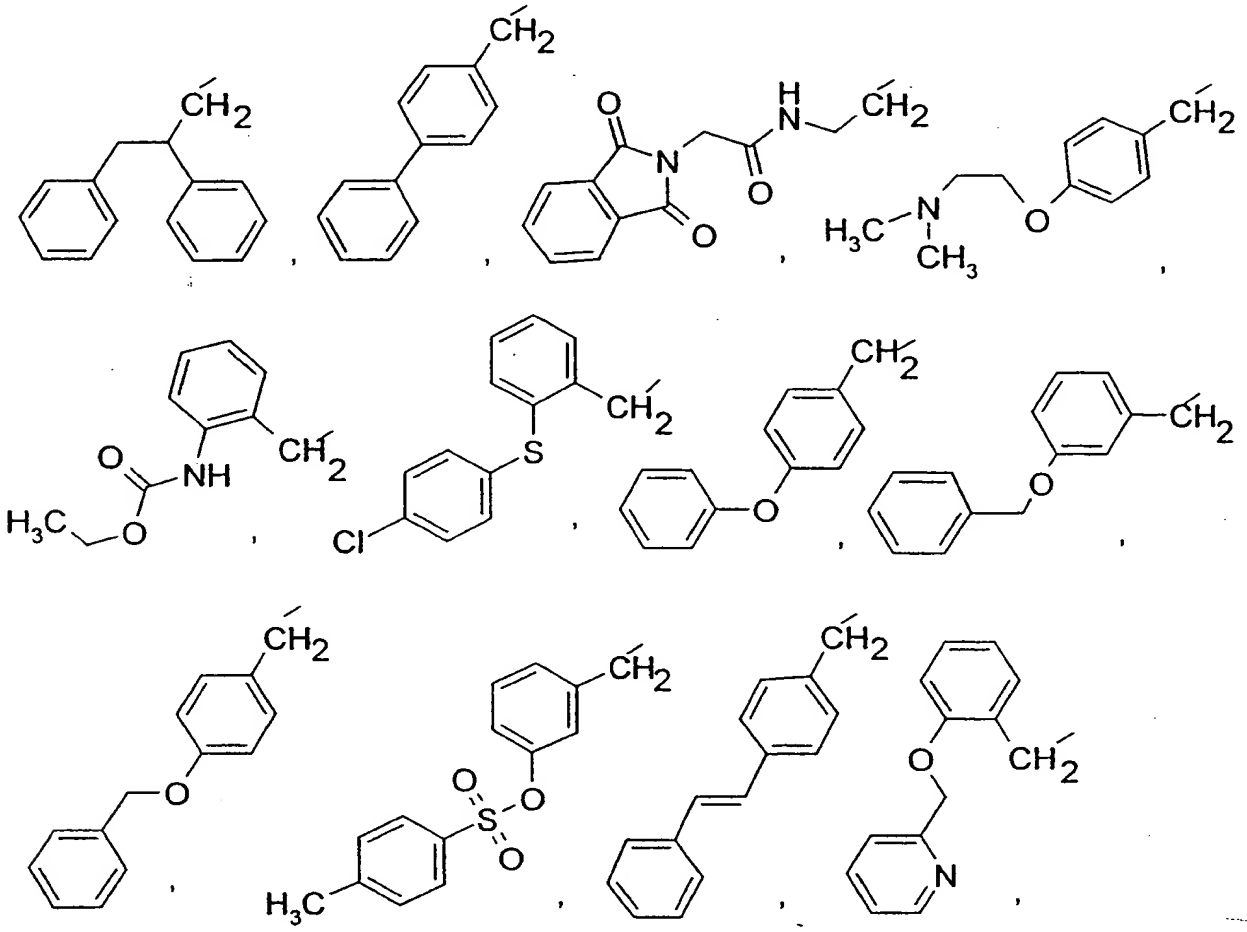
carboxy,

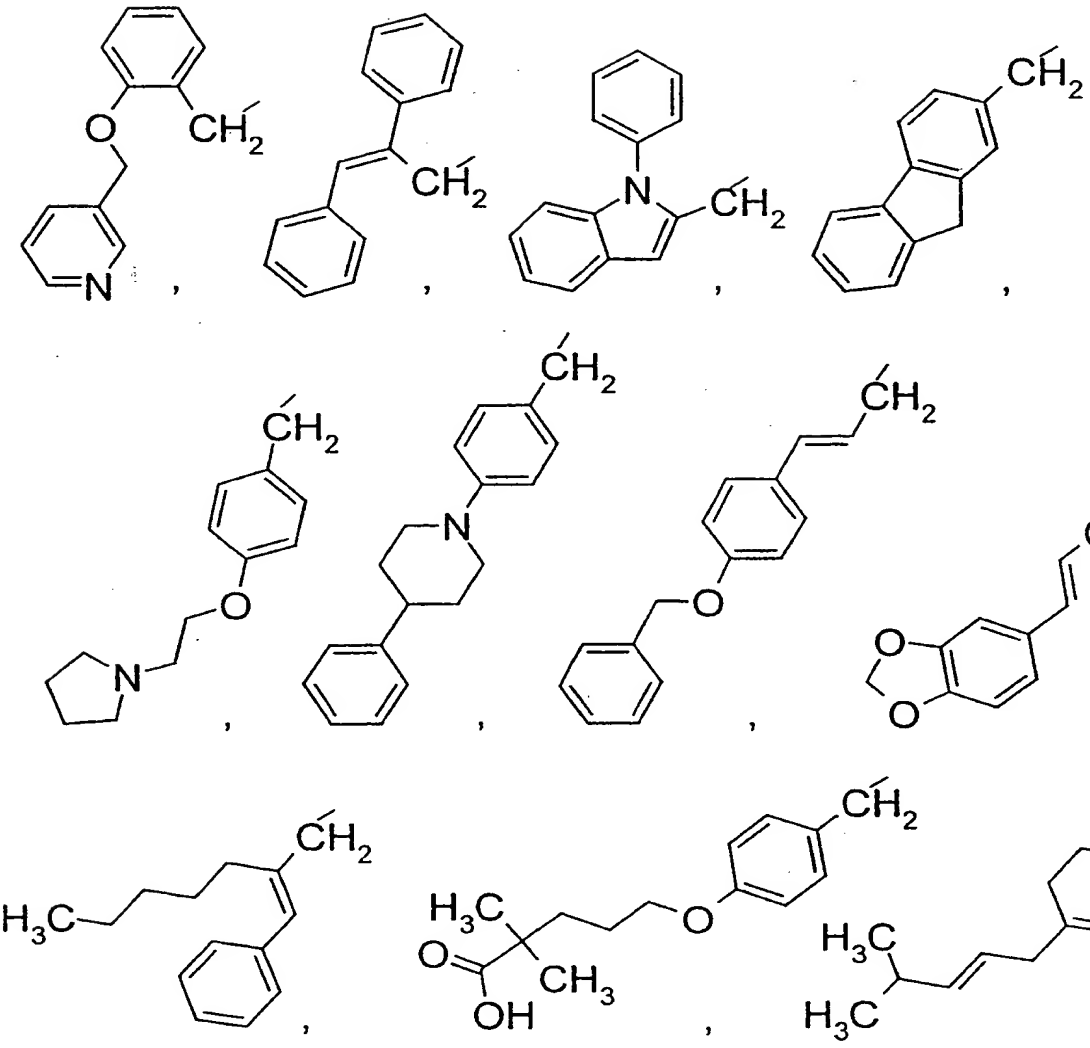
sulfonamide, or

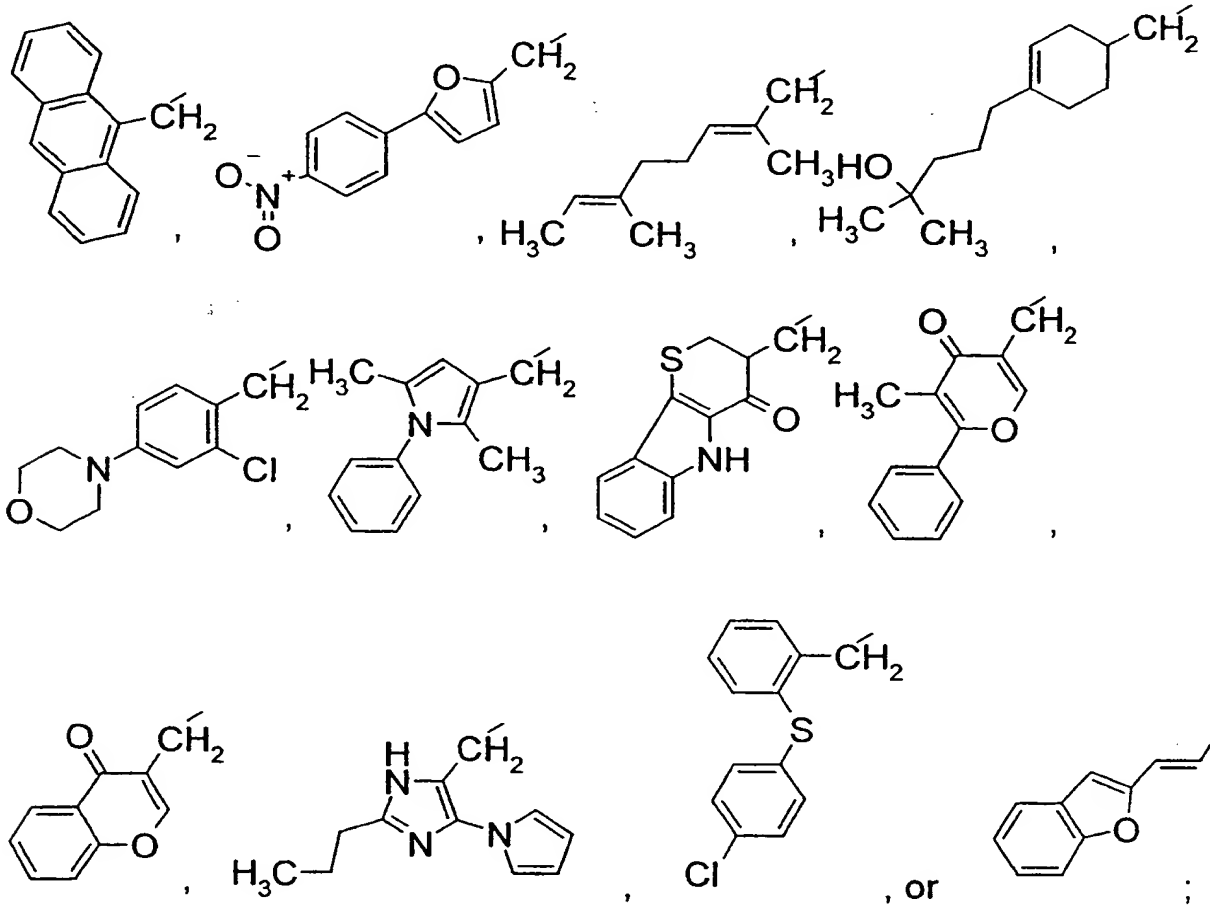
nitro;

R can also be:









R^1 and R^2 are each independently H or C_1-C_4 alkyl;

m is an integer from 0 to 3;

X is NHCONH , or NR^8 where R^8 is H or C_1-C_4 alkyl;

R^3 is hydrogen or C_1-C_4 alkyl;

n is an integer from 1 to 2;

R^4 is naphthyl or indolyl, wherein said groups are unsubstituted, mono-, di- or trisubstituted by alkyl, hydroxy or formyl;

R^9 is hydrogen or C_1-C_4 alkyl;

R^5 and R^7 are each independently hydrogen or $(CH_2)_pR^{10}$ where:

p is an integer of 1 to 3, and

R^{10} is H, CH_3, CN, OH, OCH_3, CO_2CH_3, NH_2, $NHCH_3$, or $N(CH_3)_2$;

q is an integer of 0 to 4;

R^6 is phenyl,
pyridyl,
thienyl,
furyl,
pyrrolyl,
pyrazolyl,
imidazolyl,
quinolyl,
isoquinolyl,
naphthyl,
indolyl,
benzofuryl,
benzothiophenyl,
benzimidazolyl, or
benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by

alkyl,
hydroxy,
alkoxy,
halogen,
CF_3,
NO_2,
$N(CH_3)_2$,
OCF_3,

$SONH_2$,

NH_2,

$CONH_2$,

CO_2CH_3, or

CO_2H,

or R^6 is:

straight alkyl of from 1 to 3 carbons,

branched alkyl of from 3 to 8 carbons,

cycloalkyl of from 5 to 8 carbons, or

heterocycloalkyl,

each of which can be substituted with up to one or two substituents selected from

OH,

CO_2H,

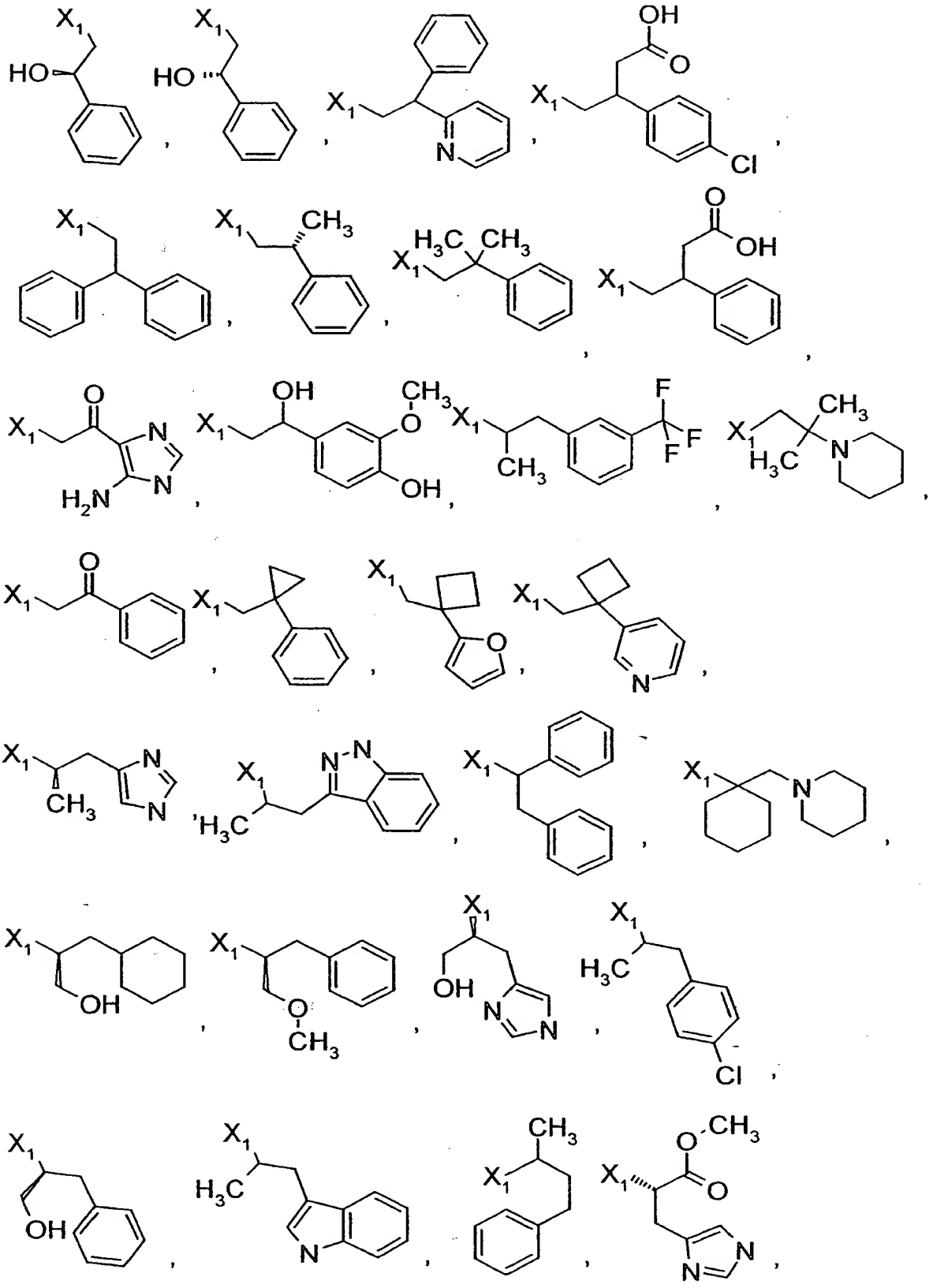
$N(CH_3)_2$,

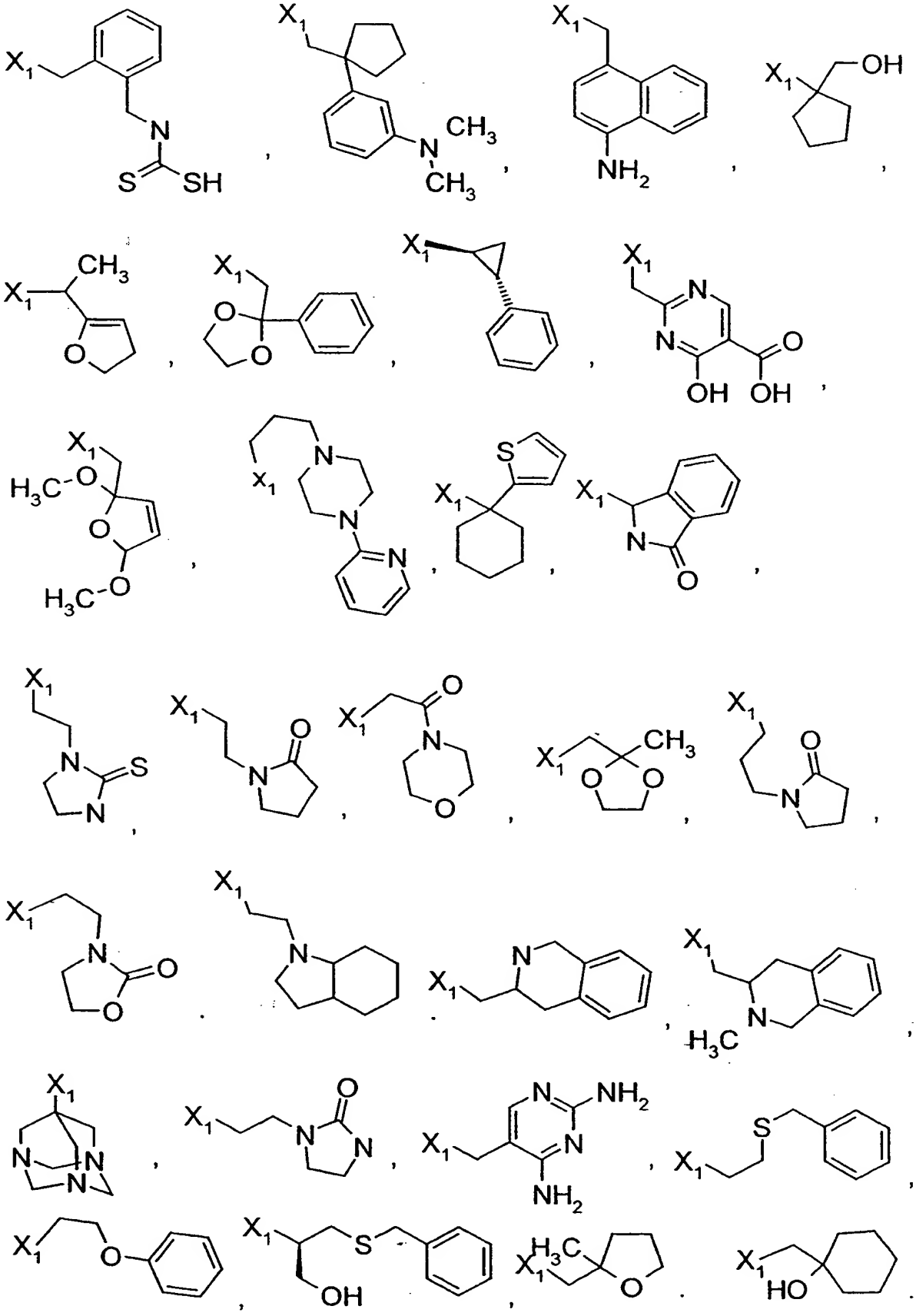
$NHCH_3$ and

CH_3; and

R^5 and R^6, when joined by a bond, can form a ring;

R^6 is also

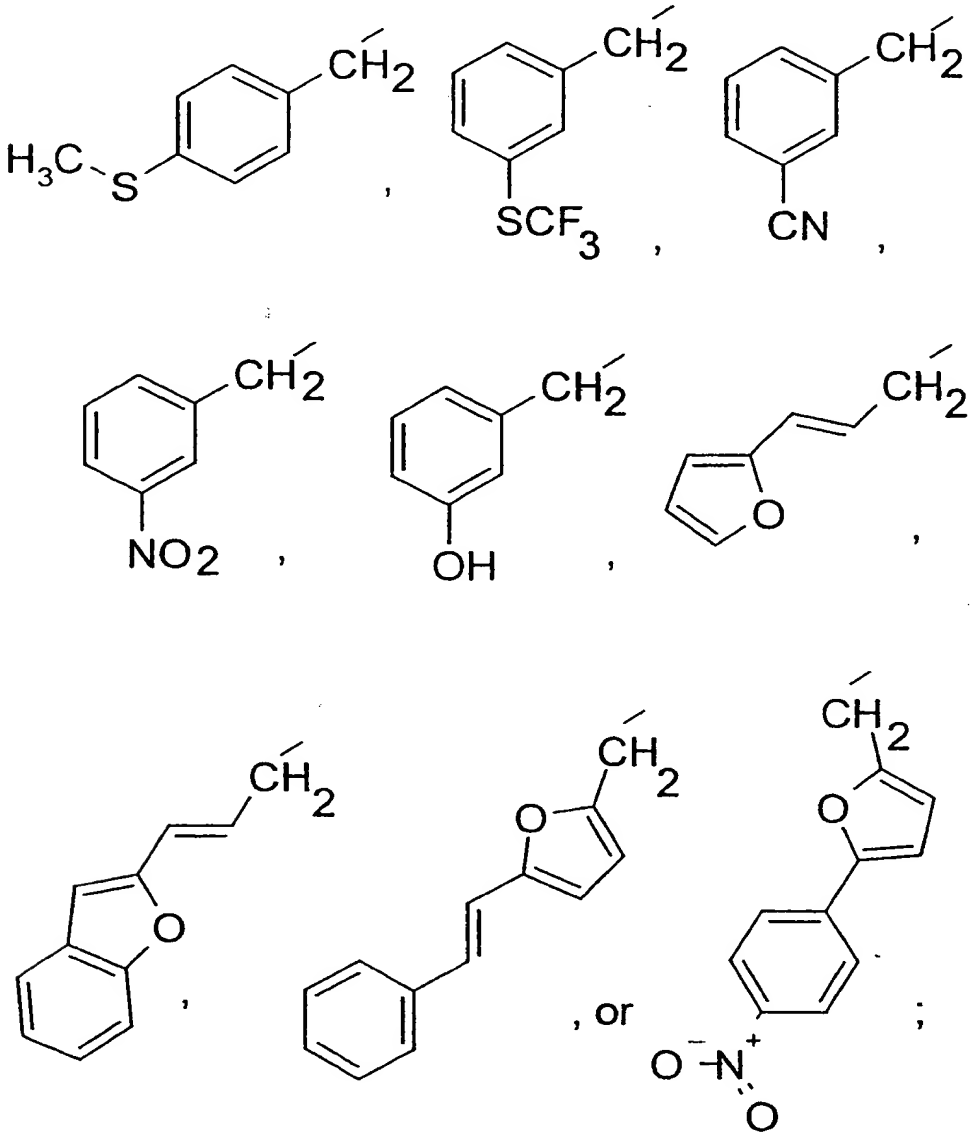




where X_1 represents the rest of the molecule.

2. A compound of Claim I wherein R is selected from :

pyridyl,
thienyl,
furyl,
quinolyl
isoquinolyl
naphthyl,
indolyl,
benzofuryl,
benzothiophenyl,
benzimidazolyl,
benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by alkyl, hydroxy, alkoxy, halogen, or CF_3.



m is an integer from 1 to 3;

R^6 is phenyl
pyridyl,
thienyl,
furyl,
pyrrolyl,
quinolyl,
isoquinolyl,
naphthyl,
indolyl,

benzofuryl,
benzothiophenyl,
benzimidazolyl, or
benzoxazolyl,
wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by
alkyl,
hydroxy,
alkoxy,
halogen,
CF_3,
NO_2
$N(CH_3)_2$,
OCF_3,
$SONH_2$,
NH_2,
$CONH_2$,
CO_2CH_3, or
CO_2H,

cycloalkyl of from 5 to 6 carbons or heterocycloalkyl, with up to one or two substituents selected from OH,
CO_2H,
$N(CH_3)_2$,
$NHCH_3$ and
CH_3 ; and

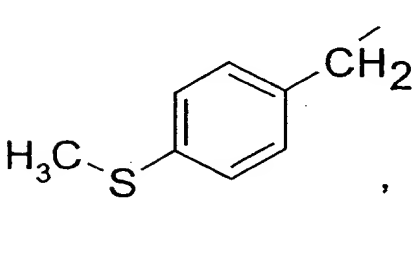
R^5 and R^6 when joined by a bond can form a ring.

3. A compound according to Claim 2 wherein R^1 and R^2 each are hydrogen.

4. A compound according to Claim 3 wherein X is NR^8.

5. A compound according to Claim 4 wherein

R is pyridyl,
thienyl,
furyl,
quinolyl,
naphthyl,
benzofuryl,
benzothiophenyl,
benzimidazolyl, or
benzoxazolyl, where each of the foregoing is unsubstituted, mono-, di- or trisubstituted by alkyl, hydroxy, alkoxy, halogen, or-CF_3 ,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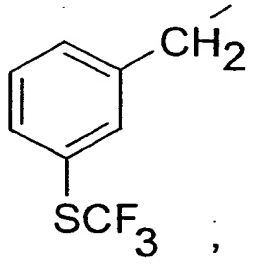
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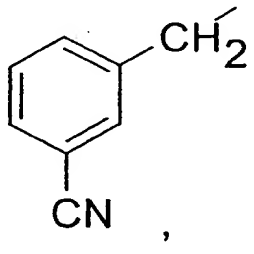
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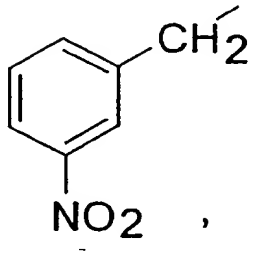
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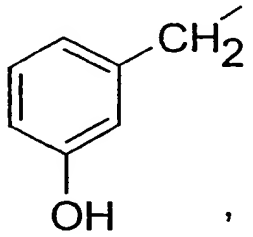
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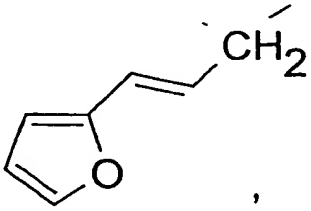
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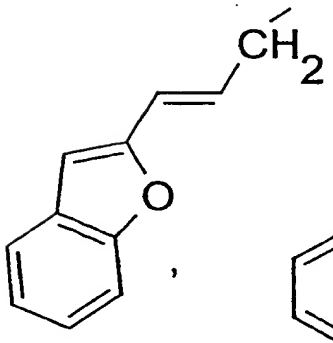
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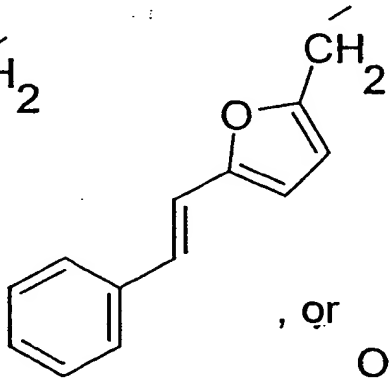
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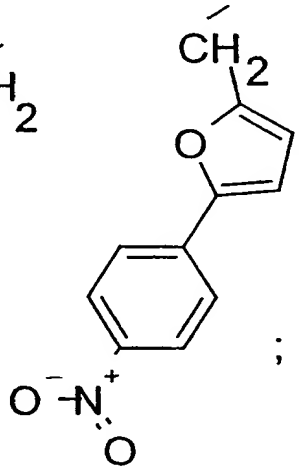

;

R^1 and R^2 are each H;

m is an integer from 1 to 3;

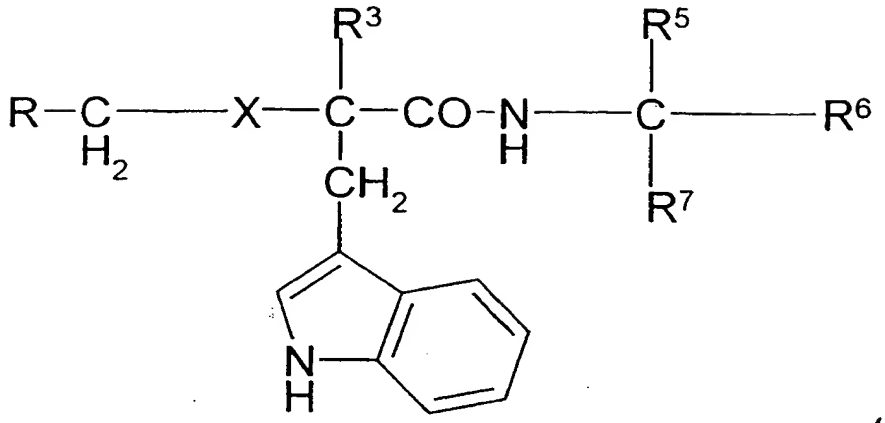
X is NR^8 or NHCONH, where R^8 is H or methyl;

R^9 is hydrogen or alkyl of 1 to 3 carbon atoms;

R^6 is phenyl,
pyridyl,
thienyl,
furyl,
pyrrolyl,
benzimidazolyl,
where each of the foregoing is unsubstituted, mono-, di- or trisubstituted by
alkyl,
hydroxy,
alkoxy,
halogen,
CF_3,
NO_2, or
$N(CH_3)_2$;
cyclohexyl or heterocycloalkyl, with up to one or two substituents selected from
OH,
CO_2H,
$N(CH_3)_2$,
$NHCH_3$ and
CH_3; and

R^5 and R^6, when joined by a bond, can form a ring.

6. A compound of the Formula II



(II)

wherein:

R is benzofuryl,
benzoxazolyl,
3-cyanophenyl,
3-nitrophenyl, or
3-trifluoromethylphenyl;

R^3 is hydrogen or methyl;

X is NH or NHCONH;

R^5 and R^7 independently are hydrogen or CH_2R^{10}, where R^{10} is H, CH_3 or OH;

R^6 is phenyl,
substituted phenyl,
pyridyl, or,
cyclohexyl;

and the pharmaceutically acceptable salts thereof.

7. A compound of Claim 6 selected from :

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-4-yl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-(4-nitro-phenyl)-ethyl]-propionamide, [R-(R*,R*)]

2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-1-phenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide, [R-(R*,R*)]

[R-(R*,S*)]2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide

[R-(R*,S*)]2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-p-tolyl-ethyl)-propionamide

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-p-tolyl-ethyl)-propionamide, [R-(R*,S*)]

2-(3-Cyano-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

3-(1H-Indol-3-yl)-2-(3-nitro-benzylamino)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-(3-trifluoromethoxy-benzylamino)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-pyridin-4-yl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

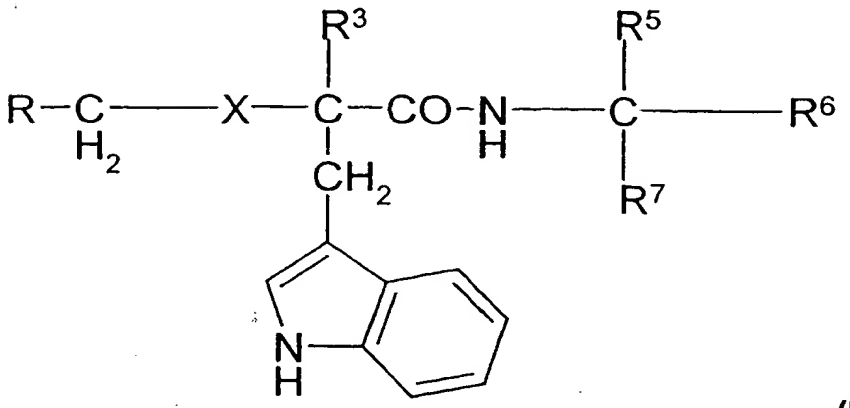
2-[(Benzooxazol-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide

2-(2-Benzofuran-2-yl-ethylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)] and

2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)].

8. A pharmaceutical formulation comprising a compound of Claim I admixed with a pharmaceutically acceptable diluent, carrier or excipient.

9. A formulation according to Claim 8 employing a compound of Formula II



(II)

wherein:

R is benzofuryl,
benzoxazolyl,
3-cyanophenyl,
3-nitrophenyl, or
3-trifluoromethylphenyl;

R^3 is hydrogen or methyl;

X is NH or NHCONH;

R^5 and R^7 independently are hydrogen or CH_2R^{10}, where R^{10} is H, CH_3 or OH;

R^6 is phenyl,
substituted phenyl,
pyridyl, or,
cyclohexyl;

or a pharmaceutically acceptable salts thereof.

10. A formulation according to Claim 9 employing a compound selected from :

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-4-yl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-[1-(4-nitro-phenyl)-ethyl]-propionamide, [R-(R*,R*)]

2-[(Benzofuran-2-ylmethyl)-amino]-N-(2-hydroxy-1-phenyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide, [R-(R*,R*)]

[R-(R*,S*)]2-[(Benzofuran-2-ylmethyl)-amino]-N-(1-cyclohexyl-ethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide

[R-(R*,S*)]2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-2-methyl-N-(1-p-tolyl-ethyl)-propionamide

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-p-tolyl-ethyl)-propionamide, [R-(R*,S*)]

2-(3-Cyano-benzylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

3-(1H-Indol-3-yl)-2-(3-nitro-benzylamino)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

3-(1H-Indol-3-yl)-N-(1-phenyl-ethyl)-2-(3-trifluoromethoxy-benzylamino)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-pyridin-4-yl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)]

2-[(Benzooxazol-2-ylmethyl)-amino]-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide

2-(2-Benzofuran-2-yl-ethylamino)-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)] and

2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1H-indol-3-yl)-2-methyl-N-(1-phenyl-ethyl)-propionamide, [R-(R*,S*)].

11. A method for antagonizing the NK_1 receptor in a mammal comprising administering a compound of Claim 1.

12. A method for treating a CNS disorder in a mammal in need of treatment comprising administering an effective amount of a compound of Claim 1.

13. A method according to Claim 12 wherein the CNS disorder is selected from pain, anxiety, depression or schizophrenia.

14. A method according to Claim 12 wherein the CNS disorder is selected from neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity, and addiction disorders.

15. A method for treating an allergic or inflammatory disorder in a mammal in need of treatment comprising administering an effective amount of a compound of Claim 1.

16. A method according to Claim 15 wherein the allergic or inflammatory disorder is selected from arthritis, asthma, bronchitis, psoriasis, eczema, rhinitis, colitis or Crohn's disease.

17. A method for treating a neuropathological disorder in a mammal in need of treatment comprising administering an effective amount of a compound of Claim 1.

18. A method according to Claim 17 wherein the neuropathological disorder is selected from scleroderma or emesis.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 99/29592

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C07D405/14 C07D413/12 C07D403/12 C07D409/12
C07D401/12 C07D209/20 C07D307/81 A61K31/405 A61K31/34
A61P25/00 A61P11/06 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 52903 A (WARNER-LAMBERT COMPANY) 21 October 1999 (1999-10-21) page 3, line 25 -page 5, line 25	1-18
A	WO 98 07718 A (WARNER-LAMBERT COMPANY) 26 February 1998 (1998-02-26) page 2, line 13 -page 5, line 25	1-18
Y	WO 95 33744 A (WARNER-LAMBERT COMPANY) 14 December 1995 (1995-12-14) page 4, line 10 -page 10, line 26	1-18
Y	WO 95 14017 A (ELI LILLY AND COMPANY) 26 May 1995 (1995-05-26) page 3, line 10 -page 6, line 30	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 2000	18/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ..tional Application No
PCT/US 99/29592

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 443 132 A (FUJISAWA PHARMACEUTICAL CO., LTD) 28 August 1991 (1991-08-28) page 3	1-18
Y	US 5 716 979 A (DAVID CHRISTOFFER HORWELL ET AL.) 10 February 1998 (1998-02-10) cited in the application column 2, line 30 -column 6, line 65	1-18
Y	US 5 594 022 A (DAVID C. HORWELL ET AL.) 14 January 1997 (1997-01-14) column 2, line 21 -column 6, line 51	1-18
Y	HONGBO QI ET AL.: "L-TRYPTOPHAN UREA AMIDES AS NK1/NK2 DUAL ANTAGONISTS" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , vol. 8, 1998, pages 2259-2262, XP004137257 the whole document	1-18
Y	DAVID C. HORWELL ET AL.: "quantitative Structure-Activity relationships (QSARs) of N-terminus Fragments of NK1 tachykinin Antagonists: A comparison of Classical QSARs and three-Dimensional QSARs from Similarity Matrices" J. MED. CHEM., vol. 38, no. 22, 1995, pages 4454-4462, XP002041962 the whole document	1-18
Y	SOLO GOLDSTEIN ET AL.: "Bioactive conformations of peptides and mimetics as milestones in drug design: Investigation of Nk1 receptor antagonists" LETTERS IN PEPTIDE SCIENCE, vol. 2, 1995, pages 125-134, XP000650996 the whole document	1-18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/29592

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-18
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 11-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte Jonal Application No
PCT/US 99/29592

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Jonal Application No
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